GENERAL
PATHOLOGY

BY

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FROM

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REVISED BY

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WITH 604 ILLUSTRATIONS IN BLACK AND IN COLORS

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PREFACE.

This revision is an attempt to present the subject of Pathology from the standpoint primarily of the needs of the medical student, while preserving the usefulness of the book as a convenient reference for the practitioner. Advantage has been taken of the fact that the book was to be reprinted to make almost numberless changes in the language of the translation, in order more simply and directly to express the views of the author, and to add a considerable amount of new subject matter, in addition to making certain needed alterations in portions of the old, including the subjects of acromegaly, Addison's disease, status lymphaticus, eunuchoidism, autolytic, amyloid and Zenker's degenerations, ochronosis, hæmochromatosis, and bronzed diabetes, carotinæmia, lipomatoses and the embryonal fat cells, ossifying myositis and multiple exostoses, the skin moles, malignant transformation of myomata, neuroblastoma, polycystic kidneys, lymphosarcoma, pseudoleukemia, Hodgkin's disease, the multiple myeloblastomata, Martland's tumor of the bone marrow and Barrie's hæmorrhagic osteomyelitis, surgical tuberculosis of the intestine, Wilms' tumor, anthrax, ascariasis, oxyuris in the appendix, trichina embryos in the blood, juvenile gangrene, the effects of the so-called pandemic influenza, botulism, the reactions to arsphenamine, a somewhat drastic rearrangement of the chapter on thrombosis, etc. Some of these changes appear in small type while others have been interpolated in the original text. The general arrangement of the book has not been disturbed, although many of the old illustrations have been eliminated. In general, these have been replaced by photographic reproductions from the wards and laboratories of Bellevue Hospital; for these I am indebted to Mr. William B. Morrison. In the same way, some of the older literature has been omitted and in its place, wherever possible, references to works in English have been substituted as more easily reached and read.

I am amply repaid for all the difficulties of the work by the consciousness that it should be helpful to the medical profession generally and especially to students of medicine, inasmuch as the book, as written by Ziegler and as modified by my distinguished predecessor, Professor Warthin, was far too valuable to be abandoned for the lack of someone to bring it up to date. I wish especially to acknowledge my debt to my secretary, Miss Martha Wirth, without whose tireless support and interested co-operation I could not well have completed the great amount of technical work involved in preparing this new edition.

DOUGLAS SYMMERS.

THE PATHOLOGICAL LABORATORIES, BELLEVUE HOSPITAL,
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AUTHOR'S PREFACE TO THE ELEVENTH EDITION.

In the preparation of this new edition I have endeavored to utilize as fully as possible the researches of the last several years, and, in so far as these have given us new facts and represent actual advances in our knowledge of pathological processes, to incorporate them into the contents of the book. It has become almost impossible to review the great mass of literature concerning the pathogenic micro-organisms, their life history, and their effects upon the human organism; but I hope that the essential and established results of recent investigations have not escaped me, and that I have estimated them at their proper worth. I may mention with especial emphasis the researches of Schaudinn on the spirochætæ and the parasites of malaria; also those of other authors on the trypanosomata, various pathogenic bacteria, the agglutinins, precipitins, cytolysins, and hæmolysins, as well as the numerous investigations and theoretic observations that, based upon Ehrlich's side-chain theory, have been carried out concerning the toxic action of bacterial products and the formation of antitoxic and antibacterial substances.

During recent years an immense amount of literature concerning tuberculosis has appeared; but our previous views concerning its etiology and genesis have not been materially altered. Koch's view as to the difference between human and bovine tuberculosis is applicable only in so far as certain differences in the characteristics of the two strains of bacilli are concerned. For all these differences it is true that bovine tuberculosis is communicable to man, and the domestic animals may become infected from tuberculous human beings. Von Behring's publication that infants may be easily infected through milk containing tubercle bacilli has only confirmed well-known views. The attempt of von Behring to refer all cases of tuberculosis to an intestinal infection occurring in infancy is doubtless an error, and is not likely to destroy the belief that tuberculosis is most frequently an air-borne infection and enters primarily through the lungs.

The researches concerning the etiology, genesis, and morphology of neoplasms have likewise been numerous and extensive; nevertheless, any expectations of a great advance in our knowledge of the etiology of neoplasms are doomed to disappointment. The attempts to establish a parasitic etiology for tumors have entirely failed, and the extensive statistics that have been amassed concerning the distribution of carcinoma have led to results that can be regarded only as antagonistic to the parasitic theory. Of greater value have been the researches on the histogenesis of tumors; yet I find in these essentially only a confirmation and a more thorough grounding of our older views. I cannot bring myself to the acceptance of all the latest views, for example, the assumption that the preliminary condition of tumor development is to be found in the isolation, disconnection, and misplacement of germinal anlage or of single cells

during embryonal or extrauterine life (Ribbert, Borrmann), or that the epithelial cells of a carcinoma can become transformed into connective-tissue cells (Krompecher).

Significant advances in the theory of fatty degeneration and glycogen deposit are also to be noted; and although many problems must still wait a solution, our knowledge concerning these processes has been greatly furthered through the labors of recent years.

The long discussion over the significance of the cells appearing in the tissues during the course of inflammation has at last reached certain conclusions. The questions still unsettled are of minor importance.

The arrangement of the book is left, on the whole, as in the last edition; but I have not simply inserted the new facts and views, many sections having been entirely recast to agree with the additions. The number of illustrations has been increased from 586 to 604. The bibliography has been given a careful revision and brought up to the autumn of this year.

E. Ziegler.

Freiburg im Breisgau, December, 1904.

Note.— Because of the difference in the size of the page it has been found necessary to reduce slightly some of the illustrations. In such cases the magnification or amplification has been changed to meet the amount of reduction.

GENERAL PATHOLOGY.

INTRODUCTION.

Physiology is the science of normal life and teaches us concerning its activities. At the same time it shows us that vital functions are performed according to laws having their foundation in structure. Changes in organic structure, *manifesting themselves as vital phenomena differing from those regarded as normal,* form the basis of **disease.** The return to the normal is known as **recovery** or **healing.**

Permanent cessation of all vital functions constitutes **death.** Temporary interruption of the vital activities without loss of the possibility of return to the normal may be seen in the condition of **apparent death** or congelation, which may be followed by either death or by return to life (anabiosis).

When pathological changes are present in the tissues, arising either before the appearance of symptoms or persisting after their cessation, so that at any time a new outbreak of the latter may take place, the disease is spoken of as **latent.**

The *science of disease* is embraced by **Pathology.** There falls to it the *determination* of *the causes and origin of pathological processes,* these two divisions constituting **etiology** and **pathogenesis.** A second task lies in the investigation of the anatomical changes underlying the alterations of function; and that branch of the science to which this is assigned is known as **pathological anatomy.** Since the finer organization of different tissues varies according to their functions, and since we cannot conceive of vital manifestations without a material substratum, it is reasonable to assume that pathological manifestations must likewise be the expression of material changes in the tissues concerned. Moreover, experience has taught us that in the case of any alteration of function in any tissue or organ, there may be demonstrated changes of structure, in part even macroscopically, while at other times they can be made out only with the aid of the microscope and by special histological methods.

A third field belonging to pathology is concerned with the *observation and interpretation of the symptoms of disease as seen in the patient,* and this branch is designated **clinical pathology, pathological physiology, physiological** or **biological pathology.** Its facts are ascertained by observation and examination of the patient, and through special physical and chemical methods. Successful application of the results obtained by the methods of clinical or biological pathology requires a **knowledge** of the **pathological-anatomical** changes present, as well as of their **etiology** and **pathogenesis.** As a further help to the interpretation of disease a **knowledge** of the *chemical processes* taking place in the living organism under the influence of the activity of cells is essential. This knowledge is specialized in the science of **pathological chemistry.**

The many-sided domain of **Pathology** demands division into various branches according to special points of view. A knowledge of *clinical pathology* is best gained at the bedside or in the clinic. Likewise *chemical pathology* requires special theoretical and practical training. In this text-book **General Pathology** will be considered as including **etiology, pathogenesis,** and **pathological anatomy.** *Chemical Pathology* will be touched on only in so far as it is necessary to an understanding of the anatomical changes in diseased organs.

CHAPTER I.

The Extrinsic Causes of and the Congenital Foundations for Disease.

1. *Deficient Supply of Food and Oxygen, Fatigue, Heat and Cold, Changes of Atmospheric Pressure, and Electrical Influences.*

§ 1. From birth to death man is exposed to the influences of the world surrounding him, many of these influences being favorable to the exercise of his functions, while others are not.

As long as the human organism is able to offset these influences, through independent changes of its relations to the world or through adaptation of its functions to external conditions, it will remain in health. If his regulating mechanism no longer suffices for successful opposition to unfavorable influences, and if he cannot escape these or change his conditions of life, man becomes ill or dies.

For its preservation the body needs a certain amount of food, water, and oxygen; and though it may exist for a short time without these, an **insufficient supply** beyond a certain limit and after a certain time must lead to disease or death.

Total deprivation or diminution in the supply of oxygen to the tissues may take place at any period of life, either because of lack of oxygen in the surrounding medium, or obstruction to the entrance of the oxygen into the lungs or blood, or inability on the part of the blood to take up sufficient. The fœtus *in utero* may be insufficiently supplied with oxygen as a result of diminished supply to the mother, premature separation or disease of the placenta, or compression of the cord, whereby the interchange of gases between maternal and fœtal blood is hindered. After birth an insufficient supply of oxygen may be due to hindrances to respiration, or the child may be so weak that its respiratory movements are insufficient to expand the lungs.

When the supply of oxygen is completely shut off, as may happen from the entrance of water or other fluid into the respiratory tract or from closure of the air-passages, the affected individual dies in a short time from **choking** or **suffocation**. Animals confined in closed chambers die as soon as the oxygen of the air reaches two or three per cent by volume, the normal volume percentage being 20.8 (Cl. Bernard, P. Bert).

If the supply of oxygen is not wholly shut off, but greatly diminished, as in carbon-monoxide poisoning, in which the firm combination of carbon monoxide with hæmoglobin prevents the taking up of oxygen by the red blood-cells, death by suffocation may take place only after several days. In gradually increasing hindrances to the entrance of oxygen and resulting accumulation of carbonic acid in the blood, as in narrowing of the lumen of the larynx through inflammatory exudates, compression of the trachea, weakening or obstruction of respiration, etc., a condition of breathlessness, cyanosis, convulsions, and disturbances of consciousness is produced, which is termed **asphyxia.**

If the taking up of oxygen is diminished in slight degree but for a long time, as in the lessened number of red blood-cells in oligocythæmia, degenerative processes characterized by fatty changes may occur in various tissues and may lead not only to disease but to death.

Total deprivation of food and water leads to rapid loss of body-weight, inasmuch as fat and albumin continue to be decomposed; death finally ensues. According to Lehmann, Müller, Munk, Senator, and Zuntz, the total amount of oxidation in starvation does not fall below that of the same individual in the fasting state under the same conditions. In animals death occurs after the loss of about forty per cent of the body-weight, about one-half being due to the waste of muscle.

The fat disappears most rapidly; even as much as ninety-three per cent may be lost. The other organs show diminution of substance in the following order: liver, spleen, testicles, muscles, blood, intestines, skin, kidneys, and lungs. The heart, nervous system, and bones show the least loss of weight; but destruction of bone-tissue does take place during starvation, as is shown by the increase of calcium and phosphoric acid in the urine, following ingestion of water. In the blood there is rapid diminution of the leucocytes (Luciani); the red blood-cells, on the other hand, may be relatively increased. The organs of animals dying from starvation show simple atrophy of the tissue-elements, particularly of the liver (Lukjanow).

After total deprivation of food and water, death occurs in man in from seven to twelve days; exercise hastens the end, ingestion of water may delay it markedly, so that individuals have been enabled through the use of water to endure a period of abstinence from food for thirty days or longer, without suffering permanent harm.

Life may be maintained for a long time on insufficient nourishment, but wasting of the body takes place which may lead to extreme emaciation, *marasmus,* or *cachexia,* and finally to death. The same thing happens when the composition of the food is unsuitable and only a portion of the necessary elements is present, so that the body is starved either in albumin, fat, salts, or water. Dogs deprived of all nitrogenous food die in from thirty-one to thirty-four days (Magendie). When the food is abundant but poor in albumin, there occur after a time (in dogs after six weeks) loss of appetite and repugnance to proffered food, with impairment of digestion and assimilation (Munk). This is especially the case when the food is lacking in fat, less so when albumin or carbohydrates are wanting.

If for experimental purposes an animal well supplied with food be **totally deprived of water**, there is rapid loss of weight followed in from eight to twelve days by death. The pathological changes found in the different organs are similar to those resulting from starvation.

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§ 2. An **unusual demand** on the **functional activity** of an organ for an **extended period** leads sooner or later to a state of **exhaustion,** which is due to the consumption of cell-substance, and to the formation of toxic products of metabolism, whereby the organ is incapacitated for extended activity. Most often the **results of overwork** are manifested in the muscles and nervous system by such symptoms as soreness and stiffness of the muscles, mental excitement, sleeplessness, loss of appetite, weakness, unnatural sweating, and sometimes elevation of temperature. Overwork of the heart may cause death. This may occur either when the heart is for a short time taxed to the limit of its power or when for a longer period it works slightly under its maximum capacity. If the exhausted tissues are permitted to rest and are supplied with an abundance of nourishment, the loss of cell-material will be replaced, the abnormal products of metabolism removed, and the part restored to normal. If a tissue be frequently subjected to excessive functional demands, and if the periods of rest are too short to admit of complete restoration, there will ultimately result a condition of permanent functional insufficiency which may manifest itself by degeneration or atrophy. For example, a muscle through overwork may become atrophic, and a brain constantly stimulated without proper periods of rest may reach such a state of exhaustion that it is incapable of performing its normal functions. Through rest and proper nourishment such a brain may recover; but beyond a certain limit the functional insufficiency may become permanent and manifest itself in anatomical changes.

Overwork of any organ is more quickly followed by fatigue and functional insufficiency if its nutrition is defective. Fatigue and insufficiency of the heart are most frequently observed when the general nutrition is lowered, as in fever, or when there is deficient oxygenation of the blood, as in poorly compensated heart or pulmonary diseases.

Finally, overwork and poor nourishment lower the resistance of the body to infection.

When the functional demands on a muscle or gland are only moderately increased, and if the nutrition is maintained in proportion to the increase of labor, the **tissue becomes hypertrophied,** and is enabled to perform increased work permanently.

Permanent **diminution** or **cessation of activity** causes in organs that normally perform a definite and constant function (muscles and glands) *loss of tissue-substance (atrophy).*

§ 3. **High temperatures** act, either by *local destruction of tissue (burning)* or by *overheating of the entire body.* The latter is possible only when the body is exposed to increased temperature for such a time that it cannot protect itself by increased heat-dispersion. In dry air of from 55–60° C. (131–140° F.) even profuse perspiration is no longer able to protect the body from overheating, and in a moist atmosphere the same is true at still lower temperatures.

If the human body is subjected to high temperature, it becomes overheated, and the condition known as **heat-stroke** results. The pulse-rate is increased, respiration is rapid and labored, the pupils dilate, and death may occur as in animals made the subject of experiment. The occurrence of heat-stroke is favored by heavy bodily labor, by interference with heat-dispersion through impermeable clothing, or by lack of water in the body.

The direct action of the rays of the sun on the head may cause cerebral and meningeal irritation, characterized by hyperæmia and inflammatory exudation, and the resulting condition is known as **sun-stroke** or **insolation.**

The local effects of heat on the skin, **burns,** are shown, according to the intensity of the heat and the time of its duration, either by hyperæmia (burn of first degree), by the formation of a blister (second degree), by tissue-eschar (third degree), or by carbonization (fourth degree). The heat produces local changes in the tissues, and kills them at a certain height or after a certain exposure.

When a large part of the surface of the body, about one-third, is burned, the individual usually dies, even though the burn be only of slight degree and eschars are not formed. The anatomical findings in fatal cases of superficial burns would indicate, when death has not resulted quickly from shock, that the cause of death is to be sought in changes in the blood and in disturbances of the circulation. The blood-changes consist in the loss of a portion of its water and in destruction of the red cells, or in such injury to them as diminish their function and give rise to a deposit of the products of destruction of hæmoglobin in the liver, spleen, and kidneys. The circulatory changes are characterized by a tendency on the part of the blood to stasis, hemorrhages, and intravascular coagulation, through which vessels of both the pulmonary and the systemic circulation may be obstructed, so that local tissue-degeneration and necroses occur in certain organs, for example, in the kidneys, liver, mucosa of the stomach and intestine, bones, and soft parts.

Low temperatures act in the same manner as high ones, in part by local injury and death of tissues, in part by refrigeration of the entire body. Severe and lasting lowering of temperature causes tissue death; after mild chilling there occur, as the result of tissue-degeneration, thrombosis, hyperæmia, and exudations which are relatively rich in leucocytes. Short refrigeration at the freezing-point is sufficient to produce degenerative changes followed by regenerative proliferation on the part of the uninjured cells. Epithelial thickenings may be produced (Fuerst) by repeated slight refrigerations (as well as by repeated slight increase of temperature). The tips of the extremities, nose, and ears are the most easily frozen. After repeated chillings of mild degree redness and swelling of the skin. associated with severe itching, often occur (*chilblains, perniones*).

If the temperature of the entire body be markedly lowered, general paralysis results from diminished excitability of the tissues, the nervous system and heart being especially affected. The sensorium becomes dulled, the heart-beat and respiration grow weaker, and finally cease. If the body be warmed, before the excitability of the tissues is wholly lost by crystalization, the power of movement in the limbs is gradually restored, and after a time consciousness returns. In man, instances of complete recovery have been observed, even after refrigeration of the body to from 24–30° C. (75–86° F.).

Besides the more severe forms of local or general lowering of the tissue temperature there may occur mild, general or local chillings, the so-called **colds,** as the result of which disease-phenomena may manifest themselves at the seat of chilling, and in distant parts. For example, after wide-spread refrigeration of the skin there may occur diarrhœa,

catarrh of the respiratory tract, or disturbances in the kidneys; after local chilling of the skin, painful affections of the deep-seated muscles. The exact relation between these phenomena and refrigeration is unknown (the oft-repeated hypothesis that they are due to hyperæmia of the internal organs caused by the chilling of the surface has not been proved), but there is no reason on this account to deny the existence of diseases caused by cold. Though many diseases formerly attributed to "catching cold" have been shown to be of infectious origin, there yet remain a number of disease conditions for which we know no other etiology than that of refrigeration. Conditions in which the skin is hyperæmic and the perspiratory function active favor the taking of cold. Many individuals appear to possess a predisposition on the part of certain tissues to the effects of refrigeration; in one person certain muscles, in another the mucous membranes may be affected.

According to many writers, refrigeration of the body increases the susceptibility to infection, so that, for example, pathogenic bacteria which may be present in the cavities of the body may, after such refrigeration, be able to exert injurious influences upon the tissues.

If rabbits are placed in well-ventilated incubators at a temperature of 36–40° C. (96.5–104° F.), the body temperature will rise to 39–40° C. (102.3–104° F.), the respiration and pulse being at the same time greatly increased in frequency. A very marked elevation of body temperature may lead in one to three days to death through paralysis of the nervous and muscular systems, the chief symptoms being increase of both respiratory and cardiac activity. If the increase of body temperature is not greater than 2–3° C. (3–5° F.), the animals may, if properly nourished, live from ten to thirty days or even longer, but they will lose in weight and ultimately die, showing before death a gradually increasing diminution of hæmoglobin and of red blood-cells. Degenerative changes, particularly fatty degeneration, occur in the liver, kidneys, and heart muscle.

According to *Pflüger* and others, all the vital processes may be brought to a standstill through refrigeration, without it being impossible for recovery to take place. *Preyer* also holds that the continuity of life may be wholly interrupted by refrigeration, and designates subjects who are thus "lifeless," but still capable of living, as *anabiotic*. Frogs are said to remain capable of life for many hours, even though the temperature be reduced to —2.5° C., at which point the heart is frozen. According to the investigations of *Koch,* such anabiosis of frozen animals is possible when only a portion of the water in the body is frozen and when the thawing process takes place slowly. In the case of rapid thawing, strong diffusion currents are set up between the water coming from the ice-crystals and the concentrated albuminous solutions of the blood and the tissues; and these currents exert a damaging effect.

According to the investigations of *J. Dewar* (*Proc. of the Royal Soc.,* London, 1900), the seeds of wheat, barley, mustard, peas, and pumpkins do not lose their germinative power when put into liquid hydrogen; that is, in a temperature of —250°. Further, the protoplasm under these conditions is not changed by the cold.

Not only do the heat-rays of the sun-light or the arc-light affect the human body, but their **chemically active violet and ultraviolet rays** also have an important action upon tissues. According to *Young, Beclard, Schnetzler, Godnew,* and others (for literature see *Sack, l.c.*), the processes of growth and regeneration are carried on more rapidly under the influence of blue and violet rays than in ordinary conditions. According to *Finsen,* variola-lesions in the skin run a more favorable course when protected from the violet rays by means of red glass. According to the investigations of *Maklakow* the violet and ultraviolet rays of the arc-light can produce a peculiar erythema of the skin, even when the heat-rays are excluded (*Widmark*). *Finsen* holds that "sunburn" is produced chiefly by the violet and ultraviolet rays. Bacteria in plate-cultures are killed within a short time by exposure to the ultraviolet rays of the arc-light. According to the investigations of *Godnew, Finsen, Möller,* and others, the violet and ultraviolet rays penetrate the skin, but are absorbed by the blood. Basing his views upon these facts, *Finsen* has treated skin diseases, especially lupus, vascular nævi, acne, etc., with the ultraviolet rays of the

sun and the arc-light. The heat-rays are excluded by means of quartz lenses and chambers of running water. A hollow lens of quartz through which water is flowing is pressed firmly against the affected area in order to exclude the blood, which absorbs the ultraviolet rays.

According to investigations by *Dreyer*, confirmed by *Neisser* and *Halberstaedter*, infusoria, bacteria, and animal tissues when impregnated with erythrosin (solution of 1:1,000–1:4,000) become sensitized to red and yellow rays, so that these rays act upon them in the same manner as the violet and ultraviolet. Since the red and yellow rays possess a greater power of penetration into the tissues, a more marked and deeper effect of irradiation can be obtained by the previous treatment of the tissues with solutions of erythrosin.

Roentgen-Rays, acting upon the skin for some time, cause at point of entrance and exit, degenerative changes affecting chiefly the epithelium, but also the connective-tissue cells. These are followed by inflammatory processes. Clinically these changes show themselves usually about fourteen days after exposure, and reach their acme after some weeks. The hair and finger-nails may be lost. If tissue-necrosis occurs, the healing of the resulting ulcer is slow and difficult. The Roentgen-rays have also been used with some success in the treatment of lupus and carcinoma of the skin. Exposures of 30 to 60 minutes are given, and repeated two or three times. After one or two weeks the cancer shows an inflammatory reaction. Healing takes place through the destruction of the tumor cells, which are especially susceptible to the action of the rays; and the resulting ulcer heals through the formation of scar-tissue and regeneration of the epidermis. In the case of carcinoma of the mamma a certain amount of destruction of the neoplasm may be accomplished, but not to the extent of cure. Recent cases have been observed of cancer developing in skin frequently exposed to Roentgen-rays.

According to investigations by *Heineke* and *Warthin*, the experimental irradiation of rats, mice, guinea-pigs, rabbits, and dogs causes, even after fifteen-minute exposures, marked destruction of the lymphoid cells of the spleen, bone-marrow, and lymph-nodes. The disintegration of the lymphoid cells is evident almost immediately after the exposure, and persists for some hours. After single exposures regeneration is rapid, but after prolonged or repeated exposures the spleen may finally become practically devoid of lymphoid cells. In exposures of this degree the death of the animal usually takes place within ten days, after it has exhibited marked symptoms of intoxication. Small animals may be rendered blind by prolonged exposures. In the use of Roentgen-rays as a curative agent in leukæmia it has been shown that the size of the spleen may be greatly diminished, the white-cell count brought to normal and the general condition temporarily improved. *Warthin* has shown that this improvement is due wholly to the destructive action of the rays upon the white cells of the blood-cell-forming organs, and that the essential disease-process is not cured. He has also emphasized the dangers of intoxication arising from the products of proteid disintegration, and has shown the occurrence of extensive degeneration and calcification of the kidneys in cases so treated. His investigations show also that slight changes occur in the renal epithelium as the result of short exposures. *Capps* believes that a leukotoxin is produced in the sera of animals exposed to the rays. *Scholz, Seldin, Philipp, Halberstaedter,* and others have demonstrated the production of azoöspermia in man and animals by means of Roentgen irradiation. Numerous cases of sterility in Roentgen-ray operators have been observed. *Bardeen* found that the death of spermatozoa is hastened by irradiation, and that spermatozoa injured by short exposures to Roentgen-rays, but still capable of fertilization, may cause the development of monsters from ova fertilized by them. He concludes that nuclear material may be so influenced by exposures to the rays that after a latent period it may show marked abnormalities in development. *Foersterling* warns against the dangers of irradiation in young children. *Edsall* has reported an instance of death following Roentgen irradiation, and the present tendency is to regard the rays as agents capable of producing serious damage to the animal organism.

According to certain observers, the lymphocyte is an important agent in the defensive mechanism against tuberculosis. A number of investigators have attempted to show that exposure of guinea-pigs to massive doses of X-ray, following inoculation with urine and other fluids containing tubercle bacilli, brings about a positive result more quickly than otherwise. *Kellert*, however, in a carefully controlled series of investigations has shown that when fluids containing no micro-organisms other than tubercle bacilli are injected, radiated guinea-pigs are found to be no more susceptible to tuberculosis than the control animals. If, however, the

injected fluids are contaminated by other micro-organisms, the radiated guinea-pigs are rendered more susceptible to secondary infection. (Journal of Medical Research, Vol. 39, 1918, p. 93.)

Becquerel-Rays act similarly to the Roentgen. Tissue-degenerations and inflammations appear in the second or third week after the exposure and reach their acme in 20–30 days (*Halkin, l.c.*). Slowly healing ulcers may be formed. Some success has been claimed in the treatment of cancer of the skin and lupus. According to *Pfeiffer, Friedberger,* and *Scholtz* the rays are bactericidal, and a portion of the active rays can penetrate the tissues to a depth of several millimetres. Roentgen-and Becquerel-rays are not, like light, heat, and electricity, special forms of undulations of the ether, but consist of extremely minute particles of matter, electrons, which are given off into space with great rapidity. In the case of the Roentgen-rays the projecting power is the electrical energy supplied to the Roentgen tube. The Becquerel-rays represent a property of certain bodies designated by Becquerel as *radio-activity*. In 1896 this investigator discovered that uranium and its salts give off rays that act upon photographic plates in the dark and are capable of penetrating bodies impervious to light. In 1898 *Madame Curie* succeeded in separating from pitchblende two radio-active bodies which were named *radium* and *polonium*. In 1899 a third radio-active body (*actinium*) was discovered by *Curie* and *Debierne*. Radium has been produced in a pure form and has been the most carefully studied. It is a new element, the salts of which are radio-active in the highest degree and project electrons into space at a velocity of 160,000 kilometres per second, at the same time giving off heat-rays. The air about it becomes ionized, that is, becomes a conductor for electrical discharges. The action of radium upon the tissues is similar to that of Roentgen-rays.

According to *Hinstedt* (*Ann. der Physik,* 1903), numerous springs, hot ones in particular, are radio-active, and it is not improbable that their special action is in part dependent upon this property.

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§ 4. Sudden **lowering of atmospheric pressure,** as in mountain-climbing and balloon ascents, may cause great exhaustion, with marked palpitation of the heart, unconsciousness, irregular breathing, and sometimes vomiting, and bleeding from the gums and lips. These symptoms depend upon *lack of oxygen* (P. Bert), the capillaries of the lungs being unable to take up sufficient oxygen from the rarefied air. Kroenecker believes that they are to be referred to disturbances of the pulmonary circulation. According to the investigations of Schumburg and Zuntz, it appears that a given amount of labor calls for a greater amount of oxygen at an increased elevation than at a lower level. The symptoms of mountain-sickness appear at a lower elevation than those of balloon-sickness, owing to the demands made upon the muscles in the former case during the climbing. During the building of the Gorner Grat Railway it was found that at a height of 2,700–3,000 metres the capacity of the laborers was diminished to a third.

According to the researches of Egger, Miescher, and others, sojourn in high altitudes leads, after a short time, to increase in the number of red cells and a greater hæmoglobin-content of the blood.

Schaumann and Rosenquist hold that the same phenomenon may be observed in animals confined for some time in bell-jars at a lower atmospheric pressure. Other authors (Schumburg, Zuntz, Gottstein) oppose this view, and maintain that the phenomenon is due either to concentration of the blood, from loss of water and to changes in the distribution of the blood, or to changes in volume of the measuring-apparatus; they endeavor to explain the favorable effects which many individuals experience from a residence at high altitudes by certain stimulating influences (greater exposure to sun's rays) which affect the nervous system and cause increased metabolism. According to Marti, *intense and prolonged irradiation* of the body stimulates the formation of red blood-cells and to a lesser degree also that of the hæmoglobin.

A sojourn in diving-bells or caissons, such as are employed in building operations beneath the water, in which the **atmospheric pressure is increased,** under certain conditions, as high as four atmospheres or even greater, causes a slight difficulty in breathing and a relatively unimportant increase of the pulse-rate. If a change be made quickly from the compressed atmosphere to air of ordinary pressure, there may occur within an hour a condition of great fatigue, tightness of the chest, ringing of the ears, cramps in the muscles, pains in the joints and limbs, hæmorrhages from the nose, ears, and lungs, dilatation of the pupils, and under certain conditions paralysis, coma, delirium, and even death after an interval of from one to twenty days (Caisson disease). The cause of these phenomena is probably to be found in the obstruction of blood-vessels of the spinal cord by bubbles of nitrogen that has been absorbed under high pressure (Hoche). According to experimental investigations of Heller, Mager, and von Schrötter, the blood, after rapid removal of pressure, contains free gas (almost exclusively nitrogen). In fatal cases associated with paralysis areas of degeneration (Nikiforoff) are found in the white columns of the spinal cord, in which individual nerve-fibres present marked changes in the form of swelling of the axis-cylinders, and disintegration of the medullary sheaths, with the formation of vacuoles in the place of the nerve-fibres that have been destroyed. If the gray matter is involved, the ganglion-cells may degenerate.

Changes in the electrical condition of the atmosphere and in the magnetic state of the earth have no demonstrable influence upon the human body; on the other hand, **electric discharges,** as lightning-stroke, may cause, in part, local lesions of the skin resembling burns, hæmorrhages in the skin, and burning of the hair, and, in part, lesions of the whole body. Under certain circumstances lightning-stroke causes laceration of internal organs, as, for example, the heart and liver. The most frequent and important effect of lightning-stroke is **paralysis of the nervous system,** which gives rise to severe dyspnœa, which may be immediately fatal, or after a few minutes or hours, or may gradually pass away after several hours, days, or weeks. Only rarely do individual nerve-trunks remain permanently paralyzed. A transitory paralysis may occur when the electrical discharge has not passed through the body, but has descended in its neighborhood.

In individuals who have been struck by lightning there may be found slight or severe burns of the skin corresponding to the points of entrance and exit of the current, and various injuries to the tissues in the course of its path through the body. The marks of the burn are for the greater part red, and form peculiar zigzag lines, the so-called *lightning figures* which soon disappear if the burns are not severe.

The passage of **powerful electric currents of high tension,** such as are generated by dynamos, through the human body, as may happen when an individual is placed in a circuit or comes into contact with an uninsulated conductor, may give rise to severe disturbances or cause death. According to Kratter, the lower limit of danger occurs at a tension of about five hundred volts. Alternating currents are more dangerous than continuous ones of the same strength and tension. When the effects are not fatal, the injured person is suddenly rendered unconscious, this condition lasting for a few minutes or several hours, and for several days afterward vertigo, prostration, headache, and palpitation of the heart may persist (Kratter). At the points of contact more or less severe burns are produced.

In fatal cases, death takes place suddenly or rarely after ten or thirty minutes. The autopsy findings, aside from the burns at the points of contact, are indicative of suffocation and hypervenosity of the blood, stasis within the thoracic vessels, and often small scattered hæmorrhages due to the direct action of the current. The cause of death is paralysis of the centre governing respiration or the heart's action.

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2. *The Origin of Disease through Mechanical Influences.*

§ 5. **Traumatic influences of various kinds** leading to **concussion,
bruising,** and **laceration of tissue** are of frequent occurrence, and act
through the tearing of tissue, through changes in tissue-organization not
recognizable by the naked eye, through rupture of blood- and lymph-
vessels, and through irritation and paralysis of nerves. The sequelæ are
represented by *necrosis, disturbances* of *circulation, inflammation,* and
regenerative proliferations. Frequently repeated *traumatism of slight
degree, such as rubbing,* may give rise to *hyperæmia* and *inflammation,*
which may lead to *hyperplastic growth of tissue.* If large quantities of
insoluble *dust particles* are continuously taken into the lungs induration
of the pulmonary tissue may develop. As a result of prolonged *pressure,*
atrophy of an organ or tissue may occur (corset-liver).

After a single or after frequently repeated trauma, there may de-
velop under conditions at present unknown to us, malignant new-forma-
tions called *tumors.* Trauma may further pave the way for *infection,*
in that the wound caused by the trauma is *infected at the time of injury*
or *is secondarily infected from without;* or that *micro-organisms pre-
viously present* in the body under conditions inhibiting their growth find
in *the injured tissues a suitable soil for proliferation.*

Traumatic influences affect, first of all, the **external parts of
the body;** but it may happen, either with or without visible injury,
that **internal organs** are injured, and the lacerations, necroses, and hæm-
orrhages thus produced, may be followed, not by inflammation and
reparative tissue proliferation, but also by malignant neoplasms, and by
infective processes.

Mechanical lesions (also thermal, electrical, and corrosive) run a spe-
cial course, if through local injury the **nervous system** becomes in-
volved. Such involvement occurs either through the direct action of
the trauma upon the central nervous system; or, by the stimulation of
the sensory or sympathetic nerves, the central nervous system may be
so affected that a number of additional nervous symptoms follow.

If direct concussion of the cranium is followed by paralysis of the
cerebral function and unconsciousness, the condition is called **commotio**

cerebri or **cerebral concussion.** This term is specially used when the trauma has produced no visible changes in the structure of the brain, or at least none of notable size.

Excessive stimulation of the peripheral nerves may cause reflex inhibition or paralysis, involving chiefly the functions of the heart and respiratory apparatus; the symptoms thus produced being collectively designated as **shock.** The most frequent causes of shock are injuries to the spinal column, abdominal contents, and scrotum, less frequently to the extremities and thorax. Further, shock may be caused by lightning-stroke, burns, corrosions of the skin; fear, and other strong emotions. Individuals whose nervous systems are in a certain condition of irritability are specially liable to shock; conditions of narcosis and drunkenness inhibit its occurrence.

Shock is characterized chiefly by diminished energy on the part of the heart and irregular breathing, which lead to decrease in the interchange of gases in the tissues and to lowering of the temperature (Roger). The consciousness is usually preserved, the skin and visible mucous membranes are pale, the pulse is small and markedly quickened, often irregular and intermittent.

Further, the individual suffering from shock may be excited, groan, shriek, and exhibit fearful anxiety associated with dyspnœa (*erethistic shock*); or he may lie quiet, with sunken countenance, and evidences of great weakness of both sensory and motor functions (*torpid shock*). In severe cases death takes place from stoppage of the heart and of respiration.

Shock, being due to the over-stimulation of the peripheral nerves, is allied etiologically to the phenomenon known as **syncope;** but the last-named condition differs essentially from shock in that its chief symptom is transitory loss of consciousness, while the functions of the heart and respiration show no marked disturbance. Syncope, furthermore, is usually preceded by prodromal symptoms, such as dizziness, ringing in the ear, and darkening of the visual field, these being absent in shock.

Not infrequently, following injury to some part of the body, there arises a more or less pronounced functional disturbance of the nervous system, which may often persist long after the local injury has healed, so that such disturbance is in no way dependent on anatomical changes in the peripheral or central nervous system, but must be regarded as a *disturbance* of *psychical origin.* Such conditions are termed **traumatic** or **accident neuroses,** and are characterized chiefly by subjective but in part by objective symptoms. To the first belong pains not definitely localized at the seat of injury, as headache, pain in the chest, backache; difficulty in movement, lassitude, inability to perform mental labor, dulness of perception, disturbances of sight, flashes before the eyes, dizziness, restless sleep, loss of appetite, and disturbances of digestion. With these last symptoms are associated psychical depression of a hypochondriacal or melancholic character, irregularly placed areas of cutaneous anæsthesia, enfeeblement of the senses of taste, hearing, and smell, motor paralysis, cramps, and hyperæsthesia, concentric narrowing of the visual field, pareses, muscular spasms, tremors, acceleration of the pulse, and tendency to sweating.

All of these phenomena depend essentially on psychical shattering of the perceptive life, a **psychoneurosis.** The condition may partake of

the nature of *hysteria,* as characterized by disturbance of the normal relation between the mental and bodily processes; of *hypochondria,* as recognized by the spontaneous occurrence of abnormal sensations; and of *neurasthenia,* which reveals itself by the production of abnormal sensations through relatively slight stimulation. If the will no longer controls the motor centres, hysterical paralyses arise; if the normal control and inhibition of the will are lost, so that unreasonable will-stimuli are created and influence the muscles, hysterical twitchings, contractures, or convulsions take place. If a nervous stimulus arising in the sensory tract fails to reach the consciousness, there follows hysterical anæsthesia; if there arise in the consciousness the images of expected or feared sensations, and if these images are intensified into actual subjective stimuli of consciousness, hysterical pains and neuralgias result (Strümpell).

Rosenbach designates as **kinetoses** those diseases which arise when energetic and continuous movements of the body in one direction are changed into the opposite direction, so that a shifting of the internal organs results. In this class belong the pathological phenomena observed in *seasickness,* and in the conditions caused by *see-sawing, whirling, movement in a vertical direction,* and *sudden stoppage of motion.* As a result of the rapid change in direction of bodily motion, the molecules which are moving in the line of the primary direction are forced to move in the opposite direction, and, according to Rosenbach, such a change is sufficient to cause more or less important molecular disturbance. He explains the symptoms of seasickness, as, for example, the abnormal secretion of the stomach, the increase of intestinal peristalsis, the vomiting, etc., as the results of purely mechanical influences on the tissues, and believes that the liver, intestine, brain, and nerve-plexuses are similarly affected through mechanical influences acting upon their protoplasm. On the other hand, *Binz* refers seasickness to an acute anæmia of the brain which causes the nausea and vomiting. A horizontal position and the administration of a water solution of chloral hydrate, which dilates the arteries of the head, have a favorable action upon the condition.

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3. *The Origin of Disease through Intoxication.*

It is difficult to give an exact definition of poison and poisoning, since the action of the substances considered in this connection varies greatly according to the dose and attenuation, as well as the method of introduction into the tissues of the body. The most powerful poisons when introduced in minute doses may not only be harmless, but may exert a beneficial or curative effect. On the other hand, substances which are not usually classed with poisons, such as the non-corrosive sodium salts, when introduced into the body in large quantities or in concentrated solutions, may produce effects which must be regarded as of the nature of poisoning. Further, poisons in certain dilutions (phenol) may serve as food-material.

§ 6. By **poisoning** or **intoxication** is meant that *impairment of health, caused by the injury to a tissue, which certain substances, by virtue of their chemical nature, are able to produce under certain conditions.* Such

substances are termed **poisons,** and are derived partly from the mineral kingdom, partly from the vegetable, and partly from the animal kingdom. They may occur in a natural state or be produced artificially from inorganic or organic substances. Many of the most important poisons are products of plant or animal life, and are formed within the tissues of the plant or animal. Other poisons belonging in the same category are derived from the decomposition of food-stuffs brought about by the growth of certain lower forms of vegetable life.

The *most important poisons belonging to the mineral kingdom or which are produced from minerals are:* metallic mercury, chlorine, bromine, iodine, sulphur, and various combinations of these substances, different combinations of arsenic, antimony, lead, barium, iron, copper, silver, zinc, potassium, sodium, chromium, etc. Of the *poisons containing carbon, which are artificially produced,* the most important are: chloroform, chloral hydrate, ether, alcohol, iodoform, carbon bisulphide, hydrocyanic acid, potassium cyanide, oxalic acid, nitroglycerin, amyl nitrite, petroleum, carbolic acid, nitrobenzole, picric acid, and aniline. It may be observed in this connection that modern chemistry is constantly producing new substances, some of which are poisons.

Of the *poisons produced by plants of the higher order,* those of chief importance are: the *vegetable alkaloids,* such as morphine, quinine, colchicine, atropine, hyoscyamine, veratrine, strychnine, curarine, solanine, nicotine, digitaline, santonin, aconitine, cocaine, coniine, muscarine, and ergotine, all of which in relatively small doses cause poisoning.

The *lower forms of plant life, especially bacteria, produce an extraordinary variety of both poisonous and non-poisonous substances, out of the food material in which they develop.* Some of these substances are similar to the vegetable alkaloids, others to the ferments, and are therefore designated *toxic cadaveric alkaloids, toxic ptomaïns, toxins,* and *toxenzymes* (compare § 11). It may happen that the blood, flesh, or any organ of a healthy animal acquires poisonous properties through the presence in it of products of bacterial growth. Examples of disease due to bacterial poisons in the food are *botulismus, sausage, meat, fish,* and *cheese poisoning.* These conditions are to be explained, in part by the growth of bacteria (*B. botulinus*) in the food and the formation of poisonous products, (§ 11); in part by the fact that germs were present in the tissues of the animal before death, and the animal having been slaughtered while diseased, the use of its flesh as food causes either symptoms of poisoning or of the same disease as that which affected the animal. Under certain conditions foods which are not spoiled may contain bacteria, and these may develop in the intestine of the individual eating the food and cause poisoning through the production of toxins, or enzymes.

According to Lombroso, the disease *pellagra,* which is of common occurrence in Italy, Roumania, and Greece, is caused by the eating of decomposed corn. The disease *kakkè* or *beri-beri,* which is endemic in Japan, is regarded by Miura and Yamagiva as due to the extended use of rice which has been spoiled in drying.

Among the *animals which normally produce poisons within certain tissues of their bodies,* the best known are: serpents, toads, salamanders, fish, mussels, oysters, scorpions, Spanish flies, and many stinging insects.

Certain forms of sea-fish are poisonous at all times, others only at certain periods, and observations have been made particularly of such fish found in Jap-

anese waters. According to *Saotschenko,* the poison of many poisonous fishes is secreted by certain skin-glands found at the roots of the dorsal and caudal fins, and may be found also in the eggs of such fish. According to *Remy, Miura,* and *Takesaki,* the poison is secreted in the sexual glands alone in the case of the poisonous fish belonging to the family Gymnodontes (tetrodons). According to *Masso,* there is found in the blood-serum of eels a toxic substance (ichthytoxin) which, when introduced into the small intestine of animals experimentally, causes symptoms of poisoning and may kill the animal. According to *M. Wolff,* the liver of mussels (*Mytilus edulis*) contains the poison; its action, according to *Schmidtmann, Virchow, Salkowski,* and *Brieger,* is similar to that of curare. *Brieger* has also shown that from the poisonous mussels there can be obtained basic substances closely related to ptomaïns, the basic products of decomposition. To what extent the production of poisons in poisonous fishes and mollusks is to be ascribed to normal and to what extent to pathological processes cannot at present be decided. From the fact that the mussels and oysters are poisonous only in certain places where the water is impure, and as the starfish found in the same localities are similarly effected, it is probable that the poisonous action of these mollusks may in part be due to their contamination with bacteria or to the occurrence of certain diseased conditions.

The *venom of serpents* is formed exclusively in the poison-glands lying in the upper portion of the corner of the mouth. It is a green or yellowish fluid and its activity is not influenced by drying or by preservation in spirits.

Snake venom, the poison of spiders and toads and of the blood of the eel and murœna, ricin (obtained from the seed of the castor-oil bean), and abrin (from the seed Abrus precatorius) show properties similar to those of the bacterial toxins (compare § 11). Snake-poison and that of the blood of the eel have also a hæmolytic action.

§ 7. **Poisons** may be divided according to their action into three groups: first, those producing local tissue-changes; second, those acting injuriously upon the blood; third, those affecting chiefly the nervous system and the heart without producing recognizable anatomical lesions.

The **poisons which cause marked local lesions** injure the tissues with which they first come into contact. If such poisons are diffused by means of the body-fluids, diverse organs and tissues may be injured; but their action is usually limited to that organ in which they are stored up or through which they are excreted, especially the liver, intestine, and kidneys.

The primary seat of injury is most often the mucosa of the upper portion of the intestinal tract and the respiratory passages, but in many cases the skin is first affected. Frequently poisons, which are employed for disinfecting, are brought into contact with wounds for the purpose of killing bacteria or preventing their growth, and in this way cause local changes or are absorbed and damage deeper tissues.

The poisons belonging to this class are those which cause tissue-changes at the point of contact, similar to those of burns, and for this reason are designated **caustics** or **corrosives**. If the action of a caustic reaches its greatest degree of severity, the affected tissue is destroyed and converted into either a dry, hard eschar, or a moist, soft slough. If the action is of moderate intensity as the result of a less concentrated solution of the caustic agent, or of incomplete action of the chemical even when applied in strong solution or in substance, or because the tissue itself is resistant as in the case of the skin, the changes produced are less severe, and are characterized by inflammation and hæmorrhage. Diverse changes are often found in the same organ, such as local sloughing (necroses), hæmorrhages, inflammations, and local hyperæmia. If the changes have existed for some time, the local eschars are surrounded by an inflammatory zone, which in the case of certain caustics may be of limited extent.

The caustic poisons are: first, the *corrosive acids,* sulphuric, nitric, hydrochloric, phosphoric, oxalic, arsenic, arsenious, osmic, acetic, lactic, trichloracetic, carbolic, and salicylic; the *corrosive combinations of the alkalies and alkaline earths,* potassium and sodium hydroxide (watery solutions of KOH and NaOH), caustic ammonia (solution of NH_3 in water), ammonium carbonate, caustic lime, and barium sulphate. In this class are also certain *corrosive salts,* chiefly of the heavy metals, such as salts of antimony (tartar emetic and antimony trichloride), salts of mercury (corrosive sublimate and red precipitate), nitrate of silver, zinc chloride, zinc sulphate, copper sulphate and copper acetate, aluminum acetate, potassium chromate and bichromate, and chloride of iron.

The *caustic poisons derived from animals* are: cantharidin, from the beetle *Lytta vesicatoria;* phrynin, the secretion from the cutaneous glands of the toad; the secretions from the poison-glands of snakes and scorpions; the secretion of the sting-gland of bees, wasps, and hornets; the secretion of the salivary glands of stinging-gnats, flies, and gad-flies; and the secretion of the poison-glands of the maxillary palpæ of spiders (tarantula)—all of which cause local necrosis, or hæmorrhage and inflammation. Many of the *higher plants* produce in their blossoms, seeds, stems, or roots substances which, when brought into contact with the tissues, cause irritation and inflammation, as, for example, daphne, different forms of *Ranunculus,* varieties of anemone *Primula obconica* (pubescent portion), marsh-marigold, different varieties of *Calla,* dragon-root, *Croton tiglii* (from the seeds of which croton-oil is obtained), buckthorn (*Rhamnus cathartica*), black elder (*Rhamnus frangula*).

The nature of the local changes which these and similar substances produce is varied, and is dependent partly on the activity of the poison, and partly on the location and manner of application. The mineral acids, solutions of caustic potash and mercuric chloride, when concentrated, cause marked tissue-eschars, associated with hæmorrhagic inflammation, especially when taken into the stomach. Through the action of acids there is marked withdrawal of the alkaline constituents of the body fluids, leading to disturbances of respiration and circulation. The venom of snakes usually causes severe local inflammation and hæmorrhages, which often extend beyond the region of the bite, and sometimes may cause widespread gangrene. There are snake-venoms, however, which produce only insignificant local changes, the general symptoms of poisoning being more prominent. The *volatile* or *gaseous* poisons affect chiefly the mucous membranes of the eye and respiratory tract (*irrespirable gases*). To this class belong especially the fumes of ammonia, chlorine, sulphurous acid, nitric oxide, nitric dioxide, nitric trioxide, osmic acid, formalin and mustard-oil. The action of these poisons is varied, often causing only transitory hyperæmia, but being able also to give rise to tissue necrosis and inflammation. The irritation of the respiratory tract gives rise to coughing, and spasmodic narrowing of the glottis may interfere with breathing.

To the local irritation and inflammation caused by these poisons at the seat of contact may be added *effects upon internal organs.* After the absorption of these poisons, those organs suffer most in which the poison is stored up or through which it is eliminated, though organs of varied structure may be affected, as well as those not concerned in the excretion of the poison. In the case of certain poisons, the changes at the point of entrance are slight and often not recognizable, the important anatomical lesions occurring in other tissues, to which the poison has been carried. Finally, a given poison may act as a *nerve and heart poison,* so that clinically the effects of this action are more prominent than the local lesion. In poisoning with *corrosive sublimate,* cell necrosis and the deposition of calcium take place in the secreting part of the kidneys, and there is also severe inflammation of the colon. The salts of *chromic acid, cantharidin,* and many *acids* cause more or less marked degenerative, inflammatory or hæmorrhagic changes in the kidney and urinary passages.

Phosphorus, arsenic, antimony, produce tissue-degeneration, particularly fatty degeneration, and hæmorrhages, in the kidneys, liver, heart, muscles, bone-marrow, and other organs, these changes being particularly marked in cases of phosphorus poisoning.

The effects of arsenic are particularly important in view of the frequency with which **arsphenamin** and related compounds are administered in the modern treatment of syphilis. *The method is by no means free from danger.* The untoward reactions of the drug are classified by Blanton (American Journal of Syphilis, 1919) as follows: (a) *Anaphylactoid reactions,* which appear during the administration of the drug, last 15 to 30 minutes, and are characterized by sensations of burning in

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the mouth, flushing of the skin, injection of mucous membranes, facial oedema, nausea, vomiting, a sensation of suffocation, sometimes ending in unconsciousness. (b) *Deferred reactions,* which appear several hours after the administration of the drug, last from 12 to 24 hours, and are characterized by chills, headaches, vertigo, nausea, vomiting, diarrhea, generalized aches and pains and, occasionally, by skin eruptions. (c) *Late reactions,* which appear after 24 hours or even later. Probably the majority of fatal cases fall into this group. Beginning with vomiting, diarrhea and fever, these patients rapidly develop headache, muscular twitchings, dilated pupils, disappearance of various reflexes and, after a brief illness, may die in coma. In fatal cases, Blanton and others have described widespread acute hæmorrhagic encephalitis. (d) *Herxheimer's reaction,* characterized by intensification of the syphilitic rash, said to be due to the sudden liberation of endotoxin or to insufficient doses; the so-called neuro-recurrences, in which neuritis develops in the cranial nerves, particularly the auditory and optic, an effect which is probably due to awakening of pre-existing processes in these localities; morbilliform skin eruptions, jaundice, and albuminuria. Moreover, the intensive treatment of syphilis by a combination of arsphenamin and mercury compounds occasionally gives rise to necrotic lesions in the liver, simulating acute yellow atrophy, and to degenerative and necrotic lesions in the kidney, associated with calcification of the dead epithelial structures, comparable to that of bichloride of mercury poisoning.

If an individual is exposed for long periods to the fumes of yellow phosphorous, there may take place an inflammation of the jaw bones leading to necrosis, but only when the occurrence of inflammatory changes is favored by other causes, such as decaying teeth. Formerly, this variety of necrosis constituted an important occupational disease, particularly in match factories, but strict attention to dental hygiene among the workers has almost completely eliminated it.

The long-continued use of *silver nitrate* may be followed by a deposit of black granules of silver in diverse tissues, the skin, kidneys, intestinal villi, and choroid plexus. In such circumstances the deposit of metallic silver in the skin gives a ghastly greyish hue to the complexion (*argyria*).

The *venom of snakes* possesses, in addition to its local effects, a paralyzing action on the nervous system and heart, and may cause death through paralysis of the respiratory centre.

Soluble salts of *lead* when ingested may cause irritation and inflammation of the intestine, with such symptoms as vomiting, diarrhœa, constipation, cramps in the stomach, associated with such nervous phenomena as anæsthesia, motor paralysis, convulsions, vertigo, and loss of consciousness. When ingested continuously for a long time, lead gives rise to anæmia (*Jores*), general disturbances of nutrition, intestinal colic, pains in the limbs, anæsthesia, motor paralysis, cerebral disturbances, and kidney disease. These disturbances are without doubt dependent upon the distribution and deposit of lead throughout the body, leading to anatomical lesions of varied nature.

The active principles of *ergot* (*Secale cornutum*), *sphacelinic acid* and *cornutin,* when taken in large doses, or when repeatedly eaten in bread, cause itching, pain, and cramps in the limbs, followed by numbness and feeling of cold in the toes and finger tips, and finally there may occur more or less extensive gangrene of the parts (*ergotism,* "*Kribbelkrankheit*"). In cases of chronic poisoning, degenerations of the spinal cord take place (*Tuczek*). The feeding of chickens with ergot causes gangrene of the comb through stasis and hyaline thrombosis in the blood-vessels. So characteristic is this change that it is employed as a test of the physiological activity of preparations of ergot intended for medicinal use. In animals fed for a long time with ergot degenerative changes are found in the central and peripheral nervous system, in the blood-corpuscles, and in the endothelium of the blood-vessels (*Grigorjeff*).

§ 8. The *poisons which affect the blood chiefly,* and are therefore termed **blood-poisons,** are partly gases and partly fixed substances. The latter are absorbed mainly from the intestine, but may also enter the body through wounds, or be injected directly into the blood-vessels. Some of the blood-poisons produce local lesions at the point of entrance; further, there may be joined to the action on the blood a direct effect upon the nervous system, which under certain conditions may cause death before the action on the blood is recognizable. Finally, it should be empha-

sized that the blood-changes produced by the poison may cause numerous secondary changes in different organs, for instance, in the kidneys, liver, intestine, and brain.

Carbon monoxide, hydrocyanic acid, potassium cyanide, and hydrogen sulphide form combinations with hæmoglobin giving rise to carbon-mon-oxide-hæmoglobin, cyan-methæmoglobin, and sulphur-methæmoglobin, inhibiting or destroying the functional capacity of the red blood-cells. They also produce an effect upon the nervous system which is most marked in the case of hydrocyanic acid and potassium cyanide. These poisons in small doses attack the central nervous system, producing death almost immediately through paralysis of the centres of respiration and circulation.

Potassium chlorate, toluylendiamin, hydrazin, nitrobenzol, nitro-glycerin, amyl nitrite, picric acid, phallin (a poison obtained from the mushroom, *Agaricus phalloides*), *helvellic acid* (poison of *Helvella esculenta*), *arseniuretted hydrogen,* and other substances cause hæmolysis of red blood-cells and lead to the formation of methæmoglobin, that is, to an oxygen combination of hæmoglobin, the oxygen content of which is the same as that of oxyhæmoglobin, but in which the oxygen is more firmly bound.

Certain *bacterial products,* called *bacterial hæmolysins,* have a specific action on the red blood-cells, leading to the production of hæmoglo-binæmia. The best known are those occurring in infections with certain varieties of streptococci.

When the blood of an animal is introduced into the blood stream of man or of an animal of another species, *specific hæmolysins* become active, that is, poisons which cause hæmolysis of the foreign red blood-cells. Recognition of this fact is of the utmost importance in view of the frequency with which the transfusion of blood from one human being to another is now employed as a therapeutic measure.

Carbon-monoxide poisoning most often results from the carbon monoxide in coal- or illuminating-gas, but may occur under other conditions, as in the case of vapors produced by gun-powder or gun-cotton. The effects of the inhalation of carbon monoxide result from the combination of the gas with the hæmoglobin of the blood and the formation of carbon-monoxide-hæmoglobin. The amount of oxygen combined with the hæmoglobin is thereby decreased, and the taking up of oxygen is reduced, even when the respired air contains only 0.05 per cent. or even 0.02 per cent. of CO (*Gruber*). The red blood-cells themselves present no changes. A rapid supply of carbon monoxide to the nervous system may cause direct injury to the nerves, giving rise to convulsions and later to paralysis (*Geppert*). In cases of long-continued poisoning the displacement of the oxygen from the greater por-tion of the red cells leads to asphyxia. If the affected individual does not die, there may result, in addition to the poisoning, severe disturbances of nutrition, occurring especially in the nervous system. The poisoning itself is characterized by headache, tinnitus aurium, vertigo, malaise, vomiting, fainting, convulsions, paralysis, and coma. The blood, as a result of the presence of carbon monoxide, becomes a bright violet or cherry-red color, so that the hyperæmic skin and internal organs also appear bright red. In many individuals who recover from the immediate effects of carbon monoxide, death occurs within ten days or two weeks and, at autopsy, char-acteristic areas of softening are to be found in the lenticular nucleus on both sides.

Hydrocyanic acid (*CNH*) is found in unstable combination in the leaves, bark, and seeds of many plants (bitter almonds, cherry- and peach-stones, apple-seeds, leaves of the laurel, bark of *Prunus padus,* tubers of many of the Euphorbiaceæ, flaxseed, etc.). *Potassium cyanide* (*CNK*) is used in many of the technical arts. The action of both of these poisons on the blood leads to the formation of cyanmethæmoglobin, which gives the blood a bright red color and produces a bright red post-mortem lividity.

Hydrogen sulphide (H_2S) is a constituent of the gas of sewers and dung-pits. When inhaled in large amounts, it may cause sudden death from paralysis of the nervous system. When hydrogen sulphide is for some time brought into contact with blood containing oxygen (as is usually the case in decomposing cadavers), a sulphur-methæmoglobin is formed, which gives a greenish color to those tissues in which it is deposited.

The poisons that dissolve the red blood-cells, with the formation of methæmoglobin, belong partly to the oxidizing substances (ozone, iodine, sodium hypochloride, chlorates, nitrites, and nitrates) ; partly to the reducing agents (nascent hydrogen, palladium hydride, pyrogallol, pyrocatechin, hydrochinon, and alloxanthin) ; and partly to substances which have neither a reducing nor oxidizing action (salts of aniline and toluidin, acetanilid). In the transformation of hæmoglobin into methæmoglobin through oxidizing substances, oxyhæmoglobin is present as an intermediate body.

The formation of methæmoglobin can occur either in the red blood-cells or in the hæmoglobin which has escaped into the blood-plasma; but the destruction of the blood-cells and the escape of hæmoglobin into the plasma are not always followed by the formation of methæmoglobin. In the case of marked destruction of red cells, as in poisoning from phallin, helvellic acid, arseniuretted hydrogen, only a portion of the hæmoglobin is changed into methæmoglobin. Hæmoglobin and oxyhæmoglobin have a red color, methæmoglobin a sepia-brown.

Large doses of *potassium chlorate* (ClO_3K) may cause death in a few hours through the destruction of red blood-cells and the action of the potassium, with the symptoms of vomiting, diarrhœa, dyspnœa, cyanosis, and cardiac insufficiency. The blood becomes chocolate-brown in color. In more protracted cases of poisoning through smaller doses, products of blood destruction are found in the spleen, liver, bone-marrow, and kidneys; and the urine may show a brown-red to black color (methæmoglobin). Delirium, numbness, coma, and convulsions occur during the course of the intoxication, showing that the central nervous system suffers severely. *Pyrogallol* ($C_6H_6[OH]_3$) produces similar effects; hydrazin ($H_2N\!-\!NH_2$) and *phenylhydrazin* cause, in addition to hæmolysis and the formation of methæmoglobin, multiple thromboses. In poisoning with *toluylendiamin* ($C_6H_5[NH_2]_2CH_3$) the chief action is the destruction of red blood-cells leading to deposits of iron-containing pigment in the spleen, liver, and bone-marrow. In cats methæmoglobin may be excreted through the urine (*Biondi*). In poisoning with *picric acid* ($C_6H_2[NO_2]_3OH$) there occurs, in addition to the blood changes and the formation of methæmoglobin, severe irritation of the central nervous system finding expression in violent convulsions. Small doses produce a yellowish discoloration of the skin and conjunctivae, simulating jaundice.

According to Kobert, *ricin* derived from the seeds of the castor-bean, and *abrin* from the seeds of *abrus precatorius,* should be classed with the hæmolytic-poisons, in that in the test-tube they cause agglutination of the red cells and the formation of a flocculent precipitate. In animals poisoned experimentally, local irritations, tissue-degenerations and inflammation, similar to those caused by certain bacterial toxins, are produced, as well as disturbances in the centres of the medulla oblongata, leading to cessation of respiration with progressive falling of blood-pressure. Tissue-degenerations, inflammation, and hæmorrhage are found, after longer action, at the point of application and in the intestine, where the poison is excreted. Degenerative changes are also found in lymphocytes, liver and kidney cells, and heart muscle.

§ 9. The last group of poisons, classed as **nerve** and **heart poisons,** is characterized chiefly by the fact that, in spite of the severity of symptoms, as shown in the form of irritations and paralyses, anatomical changes either cannot be recognized at all or are confined to structural changes in the protoplasm of individual nerve-cells, which are of similar character in the case of different poisons. This is especially the case when the poison is quickly fatal, while if the poisoning runs a protracted course, or in the case of chronic poisoning from small doses, extending over months and years, there are often found marked anatomical changes.

Of the great number of *poisons which act especially upon the nervous system* and may cause death through its paralysis, the most important are: chloroform, chloral hydrate, alcohol, ether, opium and its alkaloids, notably morphine; cocaine, atropine, hyoscyamine, daturine (stramonium-atropine), nicotine, coniine, cicutoxin, santonin, quinine, veratrine, colchicine, aconitine, strychnine, cytisin, curarine, and samandarine (salamander-poison).

Of the *heart-poisons,* digitalin, helleborin, muscarine, and phrynin (poison of toads) are of importance.

Chloroform ($CHCl_3$), when applied to mucous membranes, causes local irritation and transitory inflammation. When conveyed to the blood by inhalation or by absorption from the intestinal tract, it gives rise, after a short period of stimulation, to diminished irritability of the cerebral gray and white matter. According to *Binz,* the protoplasm of the ganglion-cells suffers slight coagulation. Death may be caused by paralysis of the central nervous system, as well as by heart-failure; the latter, however, occurring more especially when the heart is weak or degenerated. Certain individuals show a special susceptibility to the action of chloroform. The long-continued use of chloroform may cause degenerative changes in different organs, as the heart, kidneys, liver, muscles, and blood.

Alcohol (C_2H_5OH), after transitory stimulation, has a depressing and paralyzing action on the brain, at the same time causing dilatation of the capillaries of the skin, so that in intoxicated individuals severe chilling may easily occur. Death may take place suddenly, with symptoms similar to those of apoplexy; more frequently there is a gradual loss of consciousness and of sensory perception, the respiration becomes slower, the pulse small, the face cyanotic; complete coma and general paralysis forming the closing symptoms. The immoderate use of alcohol for months or years may cause degenerative atrophies of liver and kidneys associated with increase of connective tissue; further, sclerosis and atheroma of the arteries, degeneration of the brain, etc., are ascribed to the action of alcohol. At the present time it is impossible to say in what manner, how often, and to what extent these changes are dependent on the use of alcohol. Much is ascribed to the action of alcohol that is not in any way caused by it and is due wholly to the action of other injurious agents. It is certain, however, that drunkards suffer frequently from disturbances of digestion and circulation, catarrhal inflammations of pharynx, larynx, and bronchi, and of cerebral function; and that the disease known as delirium tremens, which is characterized by general muscular tremors, obstinate insomnia, anxiety, and hallucinations, is to be ascribed to alcoholism.

Opium and *Morphine* ($C_{17}H_{19}NO_2$) depress the cerebral functions, inducing sleep; in individual cases there may be a preceding period of stimulation. Large doses lead to unconsciousness, paralysis of muscles, slowing and weakening of the heart's action, contraction of the pupils, slowing of intestinal peristalsis, diminution in the exchange of gases in the blood dependent upon diminished excitability of the respiratory centre. There is no characteristic autopsy finding; the blood is usually dark and fluid, as in any variety of asphyxia.

4. *Origin of Disease through Infection or Parasitism.*

§ 10. *The entrance of living micro-organisms into the tissues, and their multiplication there with the production of pathological processes,* is known as **infection.** Since these micro-organisms take their food from the tissues, they are to be regarded as parasites.

The parasites causing the majority of the infectious diseases are now known. In those diseases in which they are not yet discovered (smallpox, measles, scarlatina, etc.) the existence of a parasite may be assumed since the diseases in question are characterized by phenomena common to other infections. It may happen that a given disease spreads from one affected individual to other individuals, giving rise to **pestilence** or **epidemic,** which may sweep through a house or city or through the land or over many lands. The spread of disease sometimes occurs by direct

passage from man to man, **direct contagion** (smallpox, gonorrhœa, syphilis, and leprosy) ; at other times, as if the causal agent of the disease clung to certain regions as a so-called **miasma** (malaria) and infected the individuals who came into its neighborhood.

The parasites that cause the infectious diseases belong, for the greater part to the **schizomycetes** or **bacteria** ; but certain of the higher plants, the **mould-fungi (eumycetes),** and the **yeasts** may also cause infectious diseases. **Animal parasites** are also represented by numerous species, belonging to the **protozoa,** to the **worms,** and to the **arthropoda.** It has been the custom to accord the animal parasites a special position, since many of them do not increase in the host in whom they live, but only pass through certain stages of development without causing symptoms characteristic of the infectious diseases. Such a distinction does not hold good, since certain infectious diseases (malaria) are caused by animal parasites. Further, in the case of many of the animal parasites a definite increase takes place within the human organism.

With the recognition that infectious diseases are caused by living *microörganisms,* the view was soon reached that contagious diseases must be caused by parasites that thrive only within the human or animal organisms ; while miasmatic diseases arose from agents living in the outer world and which occasionally gain entrance into man or animals. In the first case the microörganisms are designated *endogenous parasites,* the second *ectogenous.* It was assumed in regard to the miasmatic diseases that the microörganisms could increase either within the body or in the outer world ; but, in the latter place, only when they passed from the human or animal body into water, food, or earth.

With certain limitations this view is still regarded as correct; but, according to later experiences, its original application is not always correct, since many microörganisms that ordinarily increase only in living tissues as parasites require for their growth outside of the human body certain conditions of life that make their multiplication possible. The causal agents of measles, scarlatina, and of syphilis can develop only inside the human body ; that of smallpox, within the body of man and cattle, and we have not yet succeeded in growing them in artificial media. Tubercle bacilli ordinarily develop only in the tissues of man and certain other vertebrates ; but they may be cultivated on artificial media at the temperature of the body, and be successfully inoculated into man and other susceptible animals. Staphylococci and streptococci, which produce suppuration, anthrax bacilli, typhoid bacilli, cholera spirilla, and others grow easily in different solid and fluid media and can after artificial cultivation cause disease in man. But it should be noted that, even in the last-named cases, the bacteria concerned have not spontaneously increased in the outer world, so that, for example, water used for drinking becomes only the conveyor of the infective agent.

Malaria, which is considered the chief type of so-called miasmatic disease, is produced by a microörganism, which, outside the human body, must pass through definite stages of development in certain mosquitoes. Through the taking up of blood from a malarial patient the infected mosquitoes (Anopheles) represent the malaria-producing miasm, and man is infected through their bite, and not, as was originally supposed, through mists arising from marshes. It is also possible to produce infection with malaria by the transfusion of blood from a malarial patient to a healthy individual.

The view that certain diseases are of parasitic origin is old, and found expression in the works of *Kirchner* (1602–1680), *Lancisi* (1654–1720), *Linné* (1707–1778), and others. It was left to recent times, however, to place the theory of the parasitic nature of the infectious diseases on a secure foundation. Though several decades ago *Henle, Liebermeister* and others asserted that the peculiarities of infectious diseases could be explaini ! only by the assumption of a *contagium animatum,* the establishment of this doctrine is due to the investigations of recent years.

Climate is often held responsible for the origin of disease, and we are inclined to consider a region having a uniform temperature, much sun, and little wind as a healthy one, while one having marked variations of temperature, abundant precipitation, little sun, and much wind is regarded as unhealthy. This is true to a certain extent, in so far as invalids or individuals susceptible to the influences of weather are concerned, but a better criterion of the healthfulness of a region is the presence or absence of specific agents of disease, vegetable or animal parasites that may infect man. Such disease-producing agents may exist in affected members of the population of the region, in the drinking-water, in the earth, or in animals, etc. In the tropics malarial parasites play the most important rôle, their transmission to man being brought about through the agency of mosquitoes. Therefore, a beautiful region which seems to offer the best climate may be unhealthy; while raw, cold, and inhospitable climates may be healthy because' of the absence in them of the causal agents of disease.

§ 11. The **bacteria** are small, unicellular micro-organisms, which appear in the form of minute spheres (cocci), and fine, straight, or curved rods (bacilli and spirilla), frequently uniting in peculiar combinations. Many possess motile organs in the form of flagella. Under special conditions some of them produce spores.

From the standpoint of the physician bacteria may be divided into the **non-pathogenic** and the **pathogenic.** To the latter belong all those that are able to increase in the human and animal organism. But this classification is not altogether satisfactory, inasmuch as pathological conditions may be caused by bacteria that are not able to increase within living tissues. This rests on the fact that all bacteria, not only the pathogenic, but also the non-pathogenic, in their growth in nutritive media (albumin, peptone, gelatin), decompose these, and thereby often produce **substances that are toxic** for man and for the higher animals.

The most important of the substances produced by the decomposition of proteids are the basic **cadaveric alkaloids** or **ptomaïns, many of which are poisons for man.** For example, the toxic products neuridin, cadaverin, putrescin, neurin, and methylguanidin, the last three of which are poisons, may be obtained in pure form from decomposing meat. If these enter with the food into the human body **symptoms of intoxication** may be produced without the development of bacteria in living tissue. On the whole, their activity is not considered very great, and it is questionable whether the artificially produced poisonous ptomaïns ever arise during the processes of decomposition.

Besides the property of producing ptomaïns and other poisonous substances (for example, hydrogen sulphide), which belongs to many different bacteria, the **pathogenic bacteria** produce **other specific poisons.** The first of these to be considered are the **toxins** in the narrower sense, that is, poisonous substances which do not belong to the ptomaïns and are also not albuminous bodies (toxalbumins). They are products of secretion of the bacterial cells and can be separated by filtration from the bacteria. The most important representatives of such poisons are those produced by the *bacilli of diphtheria* and *tetanus,* both in cultures and in the human organism. The toxins are unstable bodies and quickly lose

their activity through heating above 50° C., the effect of light, and through the action of acids and other chemical substances; when dry they will stand 100° C. without injury. Their chemical structure is not known; they may be compared with the enzymes. When injected into susceptible animals, their action takes place after a *period of incubation* known as the *period of latency*. In the affected organism they cause the production of *antitoxins,* which render the toxin harmless in the organism and also neutralize it *in vitro.*

As a second form of specific poison there occur **intracellular toxins** or **endotoxins,** that is, poisons which cling to the bacterial cell and are separated from it only with difficulty. Even less is known of their nature than of the true toxins. Typhoid bacilli, cholera spirilla, and pneumococci form such poisons, and it is assumed that they are released and become active after the destruction of the bacteria in the human organism (bacteriolysis).

A third form of poison is found in the **bacterial proteins,** that is, the substance of the cell itself. They produce chiefly a local effect, finding expression in inflammatory reactions. It is probable that such reaction occurs in all bacterial infections in which the bacteria develop locally. If the bacteria concerned produce antitoxins the action of these is combined with that of the bacterial proteins.

In individual cases it is often impossible to decide to what extent ptomaïns or specific bacterial toxins and proteins are concerned in the production of pathological conditions. The term **toxin** is often used to cover all of the poisonous substances produced by bacteria.

Some **pathogenic bacteria** increase first in the *outer world* (for example, the tetanus bacillus), and only occasionally develop in the human or animal body; other forms develop *ordinarily only in the human or animal organism* (tubercle bacilli, glanders, leprosy, diphtheria, and influenza bacilli) and need for their development outside of the body special nutritive media, or, indeed, they cannot be cultivated at all. *Still others increase with energy in human and animal tissue, but are also easily grown upon nutritive media* (streptococcus, staphylococcus, anthrax bacillus, typhoid bacillus, cholera spirillum), and are able to multiply under natural conditions in the outer world.

The distribution of pathogenic bacteria from the affected individual to the outer world takes place through coughing, sneezing, expectoration, speaking, through intestinal and urinary discharges, secretions from wounds, sloughing of tissue, etc. When thrown into the air they may float for some time and be carried to a distance, but, sooner or later, become attached to some object. Through drying and sunlight many are quickly destroyed. Others remain alive for a period, often a long time, especially in the form of spores, and may be found in either a dry or moist state, in the water or earth. If they find the proper food-material and if the temperature is favorable they may multiply.

From the place where they are thrown down, or from the objects to which they cling, or where they have undergone development, the bacteria may suffer a wider distribution. Strong currents of air may carry them away, especially from the objects to which they cling, or in the dust of the room or of the street. Many of them are brought to the human and animal organism through food and drink, through the air, or through contamination of the fingers.

The **avenues of entrance for bacteria** are, in general, the mucous membranes of the intestinal canal, respiratory tract, the conjunctiva, the alveoli of the lungs, and open wounds. But it should be noted that many bacteria are able to enter only through certain tissues, for example, the typhoid bacillus and the cholera spirillum gain entrance only from the intestine. Through recent wounds, both pathogenic and non-pathogenic bacteria are rapidly taken into the lymph and blood; while through wounds showing healthy, granulating surfaces, the entrance of bacteria into the tissues is hindered. Pathogenic bacteria (pus cocci) not infrequently enter through the skin, either by way of the hair-follicles or the sebaceous or sweat-glands. Under certain conditions (coitus, surgical operations, dribbling of urine, childbirth) infection may take its start from the mucous membranes of the uro-genital tract. Some infections are transmitted by insects, which have taken up bacteria from the blood or secretions of a diseased individual or animal, or, having become contaminated externally, infect an open wound by scraping the bacteria from their legs, or by the introduction of germs into the skin or mucous membranes during the act of stinging or sucking. If meat containing bacteria be eaten, and if the animal while alive were affected by an infectious disease to which man is susceptible, this particular disease may thus be transmitted.

If **toxic bacterial products** enter in consideral amount into the intestinal canal or wounds at the same time with bacteria, the symptoms of **intoxication** may be produced without infection, that is, without increase of the bacteria in the tissues. This may also happen when bacteria producing such poisons develop in the contents of the intestine, in wound-secretions or in necrotic tissue, and increase as *saprophytes.* Strictly speaking, we cannot regard this as an infection, but as an **intoxication;** although it is not always possible to draw a sharp line between intoxication and infection, since bacteria originally developing as parasites not infrequently penetrate into the tissues and multiply.

Intestinal intoxications dependent upon bacterial toxins occur when meat or fluids in a condition of bacterial decomposition has been eaten as food. To such intoxications belong the affections designated as *meat-, sausage-, fish-,* and *cheese-poisoning,* in which the poison is either taken as such into the intestinal canal, or is formed there. Likewise, vegetables in a condition of fermentation and decomposition, for example, cabbage, peas, beans, corn, rice, etc., may exert a harmful influence on the intestine or on the entire organism, especially when they have been eaten in large amounts or for a long period.

If bacteria which have entered the body through one of the above-mentioned avenues are pathogenic, so that they give rise to **infection,** they may increase first at the point of entrance, in the intestinal mucous membrane, in a wound, in the skin, etc. The **local effects** of their growth depend on the individual characteristics of the bacteria, as well as on the peculiarities of the affected tissue. In general, the local action is characterized by tissue-degenerations, necrosis, inflammation, and new-formation of tissue, so that it is possible in many cases to determine the specific nature of the infection, that is, the species of bacteria causing it, from the character of the local changes. It is however, difficult or impossible to determine in every case the mode of action of the multiplying bacteria; in general, it may be said that the processes of chemical metamorphosis excited by the multiplication of the bacteria produce certain

changes in the tissue-cells, in that different substances of active chemical nature either kill the cells, or at least induce degenerative changes in them, or excite increased cell-activity. In the further development of the process the substances derived from dead and dissolving bacteria may also react on the surrounding tissue. In a sense, therefore, there occurs through the growth of bacteria a *local intoxication,* which is of greater significance than the *withdrawal of nutritive material* through the consumption by the bacteria of food substances. The latter is, however, not without significance, inasmuch as the chemical changes produced by the bacteria in the tissue juices often render these unfit for the nourishment of the tissue-cells.

The **participation of the body as a whole** in a local bacterial infection may be slight or absent, so that the disease remains a purely local affection (tuberculosis). In other cases the toxins and toxalbumins formed at the focus of infection are absorbed into the blood, and a **general intoxication** (*toxinæmia*) is produced. In such diseases as tetanus and diphtheria the sytemic reactions to local poisoning are especially prominent.

If healing does not take place at the primary seat of infection, the neighboring tissues may be involved by **invasion of bacteria by continuity.** Often the **bacteria gain entrance to the lymph-vessels or blood-channels** (*bacteriæmia*), and in this way are transported over the entire body. The result of this *metastasis of bacteria* is the production of a **lymphogenous** or **hæmatogenous infection;** that is, secondary *foci* of disease *identical in character with those at the primary seat of infection* are formed at a distance. In certain diseases (tuberculosis, suppuration, plague) the number of **metastases** is usually great, so that many parts of the body (lymph-nodes, liver, lung, brain, muscles, bones, kidneys, etc.) contain diseased foci. In other infections metastasis of bacteria from the original focus to other organs does not occur (tetanus, diphtheria), or the transported bacteria cause changes of a milder type (typhoid fever).

The entrance of bacteria into the blood constitutes the condition known as **bacteriæmia.** During transportation through the blood-vessels, there is usually no increase of the bacteria, the *blood serving merely as a vehicle,* multiplication occurring at those points where the bacteria come to rest. Nevertheless, in certain infections (anthrax) the *bacteria increase enormously in the circulating blood.* Through the obstruction of small blood-vessels by the multiplying bacteria, there may be added to the symptoms of intoxication local disturbances of circulation.

The metastasis of bacteria or toxic substances, or both, from a localized seat of infection, and the production of secondary foci and symptoms of intoxication, gives rise to the condition termed **sepsis.** According to the predominant symptoms there may be distinguished *septicæmia, pyæmia* and *lymphangoitis.* Through the combination of both the latter with septicæmia, *septicopyæmia* is produced. Originally the designation **septicæmia** was applied to those cases in which localized infection was associated with *intoxication* caused by bacterial poison without the spread of bacteria through the body. At the present time, septicæmia is used to designate the condition characterized by the entrance of bacteria and their poisons into the blood, a coincident *toxinæmia* and *bacteriæmia;* indeed, by many authors *toxinæmia* is separated from *septicæmia.*

The term **pyæmia** is employed to designate that condition in which the metastasis of pyogenic bacteria gives rise to the formation of *metastatic abscesses* at the point of lodgment.

In **septicopyæmia** the symptoms of toxinæmia and bacteriæmia are combined with the formation of metastatic foci. **Lymphangoitis** is an *inflammation of the lymph-vessels and their surroundings* caused by transported bacteria.

Sepsis is most frequently caused by the true *pyogenic organisms, staphylococcus pyogenes aureus,* and *streptococcus pyogenes,* but similar conditions occur in infection with the *pneumococcus, typhoid bacillus, colon bacillus, plague bacillus,* etc.

If **bacteria** are deposited secondarily in the body-passages which are lined with mucous membrane, as in the respiratory or urogenital tract, **they may multiply within these tracts** and produce their characteristic pathological changes. Likewise, they may **multiply within the large body-cavities,** in the peritoneal, pleural, and subarachnoid spaces. In the case of infection occurring in a pregnant woman, several varieties of **bacteria** (anthrax, glanders, typhoid, the pyogenic bacteria), may be **transmitted to the fœtus.**

The description above given of the course of an infection may be taken as a general type, and many infections run such a course; but there are many deviations from this scheme. In the first place, it not infrequently happens that in an infection which in general runs a typical course, the primary seat is not demonstrable, either because no changes occurred at the point of entrance, or because the changes produced have since disappeared. Such forms of infection are known as **cryptogenic;** they may be **lymphogenous** or **hæmatogenous.** It is typical of many infections that the primary localization of the cause of the disease is not recongnizable, so that *general* symptoms *occur before local changes are demonstrable,* and the tissue-changes occurring later have more the character of a *secondary localization of the poison of the disease.* This occurs in a number of infectious diseases, the causes of which are unknown to us; for example, in scarlet fever, smallpox, and measles; yet in many infections whose causes are known we are not always able to discover at what point the first multiplications of the bacteria occurs. Thus we know that in relapsing fever the spirilla are found in the blood in large numbers at the time of the fever, but the place of their multiplication is unknown to us.

Not infrequently a **secondary infection** may be joined to one already present. In many cases the association is accidental, in other cases the anatomical changes produced by the first infection cause a local predisposition to the new invasion. To the first group belong, for instance, croupous pneumonia occurring in an individual suffering from tuberculosis of the kidney or bones; while infection with cocci causing suppuration and septic intoxication during the course of typhoid, influenza, diphtheria, scarlet fever, dysentery, ulcerating tuberculosis, etc., may be regarded as due to the production of local tissue-changes favoring the entrance of such bacteria. These secondary infections usually aggravate the sufferings of the patient in that a new disease is added to the one already present; but it may also happen that the microörganisms entering secondarily grow only as saprophytes in exudates or in tissues killed by the first infection. In certain infections, as, for example, in

many purulent processes, the tissues may contain, even at an early stage, two or more varieties of bacteria—a **mixed** or **double infection.** The associated bacteria can persist in their association and in common excite pathological changes; but they may also become separated from each other, so that one microörganism gains a wider distribution than the other.

It has been known for many years that during decomposition poisonous substances are formed. As early as 1852 *Beck* observed that ammonia hydrothionate, which occurs in pus, possessed septic properties when injected into animals. *Panum,* in 1863, obtained from decomposing material a *putrid poison,* that is, a body not destroyed by boiling and evaporation, which possessed an action similar to that of snake-poison and the vegetable alkaloids and caused in dogs salivation, dilatation of the pupils, diarrhœa, fever, and severe prostration. *Von Bergmann* and *Schmiedeberg* obtained from decomposing yeast a crystalline body, *sepsin,* which in animals produced the symptoms of intoxication. *Senator, Hiller,* and *Mikulicz* extracted from decaying tissue-masses by means of glycerin a substance which likewise possessed a septic action. *Billroth* called this poisonous substance *putre-factive zymoid.* *Selmi* endeavored to characterize all these substances more minutely, and obtained from different constituents of cadavers extracts, partly soluble in ether, partly in water, which he recognized as fixed bases of alkaloid-like character, and which he designated **cadaveric alkaloids** or **ptomaïns.** *Gautier, Etard, Zuelzer, Sonnenschein, Béchamp, Schmiedeberg, Harnach, v. Nencki, Otto, Angerer,* and others also found in decomposing tissues similar alkaloids, which in experiments on animals were partly inert, and partly toxic, producing in the latter case symptoms of poisoning similar to those of curare, morphine, and atropine. To *von Nencki* (1876) is due the honor of being the first to obtain a cadaveric alkaloid in pure form and to establish its formula; this was accomplished in the case of collidin, obtained from decomposing glue and albumin, its platinum salt crystallizing in flat needles. Following *v. Nencki, Etard, Gautier,* and *Baumann,* and especially *Brieger,* studied ptomaïns, the last named having obtained a large number of them in a pure state and determined their physiological action. For instance, *Berger* obtained from fibrin peptone a poison (peptotoxin) which in animals causes symptoms of paralysis and ultimately death. From decomposing horse-flesh he extracted three substances crystallizing in needles, namely, neuridin, neurin, and cholin, the second of which is markedly poisonous, and, like muscarine, causes salivation, disturbances of circulation and respiration, contraction of the pupils, and clonic convulsions. From fish-flesh he obtained, besides neuridin, other poisonous bodies: ethylendiamin, a substance similar in its action to muscarine, and a substance called gadinin. From decomposing glue and cheese he obtained the poison neurin, and from decomposed yeast dimethylamin.

The majority of ptomaïns are not found in fresh tissues, and it is therefore probable that they are derived from the splitting of chemical combinations present in the tissues. Thus it is probable that cholin is formed from the splitting of lecithin, and by the further decomposition of cholin the poison neurin is formed. Cholin and neuridin are, according to *Brieger,* demonstrable in the fresh human brain.

After the poisonous nature of part of the ptomaïns had been made known through the researches mentioned above, there was developed the *hypothesis* that the toxic symptoms observed in infectious diseases could be entirely, or in a great measure, ascribed to the action of the toxic ptomaïns. Through the investigations of recent years (*Roux, Yersin, Buchner, Briegcr, C. Fraenkel, Pfeiffer, Ehrlich, Wassermann,* and others) it has been shown that besides the ptomaïns there occur **specific bacterial poisons,** which are characteristic for the given bacterial species. These were first regarded as active albumin bodies and were called **toxalbumins.** Investigations of the poisons formed in diphtheria, tetanus, cholera, typhoid fever, pneumonia, and tuberculosis have shown that the so-called toxalbumins are not albumin bodies, and have led to the differentiation of different poisonous substances as given in the text above.

The **toxins,** in the strict sense, may be compared, according to their origin, with the **enzymes** formed by the body cells (pepsin, trypsin, ptyalin) which produce hydrolytic splitting. On the other hand, the **endotoxins** clinging to the cells may be compared with the expressed juice of yeast known as **zymase** (*Buchner*), which is able, in the same way as the living protoplasm of the yeast-cell, to excite

alcoholic fermentation in fluids containing sugar. Toxins and enzymes are mixed with albuminous substances which up to the present time have not been separated from them. This explains why they were earlier regarded as albuminous bodies. *Brieger*, who first characterized the toxic substances as toxalbumins, has himself prepared toxins that gave no albumin reaction.

According to the views of Ehrlich, only those substances are **poisons** that possess a chemical affinity for some element of the body and through their union with this element cause an injurious action that may be recognized clinically (toxophorous affinity). A **toxin** or **haptin** is, according to him, a poison which possesses *two specific atomic groups,* a *haptophore group* which permits the union with the body cells through the *haptophorous group* of the latter, and a *toxophore group* which exerts the poisonous action. If in any poison the specific action of the toxophore group is lost, while the haptophore group remains, there arise **toxoids** or **non-poisonous haptins** which may anchor themselves to the body cells but are no longer poisons. Finally, there occur also primary bacterial products (in diphtheria), the **toxons** (*Ehrlich*), that is, poisons which have the same haptophore group as toxins but a less active toxophore group.

Since the *intracellular toxins,* the **endotoxins** (typhoid bacilli, cholera spirilla, B. pyocyaneus, pus cocci), are stored in the bodies of the bacteria, the bacterial cell-substance is the most active. In old cultures the poisons pass into the fluid, but they probably no longer represent the primary endotoxin, but a modification.

Cholera spirilla, typhoid bacilli, and pneumococci form endotoxins, which on the death of the bacteria are set free, and become active as such, or act in a modified form at the same time with the **bacterial proteins.**

Anthrax and tubercle bacilli probably form no true toxins, but contain poisons of another kind whose action is combined with that of the bacterial proteins.

The importance and the course of an infection depend, therefore, upon the character of the cells possessing receptors for the given toxin. In tetanus it is the nerve-cell; in tuberculosis the connective-tissue cell. Diphtheria poison does not injure the skin of the mouse, while the one-hundredth or one-thousandth part of the same dose will produce tissue-necrosis in the guinea-pig (*Ehrlich*).

Aggressins: When bacteria are grown in the pleural or peritoneal cavities, in pleural or peritoneal exudates, blood-serum, or even in distilled water, there is formed a substance which, when the non-toxic sterilized culture fluid is inoculated at the same time with a sublethal dose of the bacteria, neutralizes the protective powers of the body and permits the growth of the bacteria. These substances have been called *aggressins,* and are regarded by some as serving the bacterial organism in the same way that opsonins protect the animal body. (*Bail: Arch. f. Hyg.,* 1905.)

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§ 12. The **pathogenic moulds (eumycetes) and the budding fungi** belong, as do the schizomycetes, to the non-chlorophyllaceous thallophytes. They occur in the human organism in the form of jointed or non-jointed and sometimes branching threads or *hyphæ,* and short oval cells, the so-called *conidia.* The eumycetes may be divided into the moulds, the fungus of thrush, and the cutaneous mould-fungi. At times they form fructification organs of peculiar structure. The single cells are larger than those of the schizomycetes. Outside the body the *moulds* develop as velvety films of different colors, on the surface of many organic substances and fluids, from the carbon-compounds and salts of which they derive their nourishment. The *yeast-fungi* are found chiefly in fluids containing sugar, and are the cause of alcoholic fermentation.

The spores or conidia, which represent reproductive elements, are for the greater part formed in special organs of fructification, but may also be developed by a simple process of constriction of the ends of the hyphæ, and pass into the air from the surface of the mould-film. Likewise, yeast-cells may be carried in the air, in the case of evaporation of a fermenting fluid and the conversion of its residue into dust.

The moulds may, as do the bacteria, *produce poisonous substances in the nutritive media in which they multiply,* usually outside the human body, and when these are taken in with the food **symptoms of intoxication** are produced. For example, the chronic disease, known as *pellagra,* which occurs particularly in Italy, Spain, southwestern portions of France, Roumania and certain Southern States, is characterized by gastro-intestinal disturbances, changes in the skin, spinal and cerebral disturbances, and marasmus, is, according to one view, the result of the eating of corn which has been spoiled through the growth of certain moulds. According to Ceni the active poisonous substances are produced in the spores of the fungi.

As parasitic agents causing disease the moulds and the yeasts cause, as a rule, *local infections* characterized by tissue degeneration and inflammation.

The *moulds* develop in regions accessible from without, in the skin, the crypts of the tonsils, the ear, mouth, lungs, etc. They usually occur as saprophytes in cerumen, necrotic lung tissue, etc., but may also penetrate living tissue.

The *thrush fungus* occurs chiefly in the epithelium of the upper layer of the mucosa of the alimentary tract, but often penetrates into the connective tissue and causes inflammation. Hæmatogenous metastasis is rare.

The *cutaneous moulds* multiply in the epithelium of the skin and give rise to such lesions as favus, herpes tonsurans, pityriasis versicolor, and erythrasma.

The *yeast fungi* develop most frequently in the stomach, particularly after the ingestion of fermenting fruit juices. In glycosuria they may multiply in the urinary bladder and excite fermentation of its contents.

Yeast-like budding fungi occur also in a granulomatous and suppurative process affecting the skin and internal organs (blastomycetic dermatitis, blastomycosis, saccharomycosis, coccidioidal granuloma, etc.). The majority of the cases have occurred in America. The parasites involved cannot at present be definitely classified. By some writers (*Ricketts*) they are believed to belong to the genius Oïdium (*oidiomycosis*). Blastomycetes are supposed to be the cause of a peculiar suppurative disease in horses.

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§ 13. The **production of disease by animal parasites** is most fre-
quently brought about by the introduction of mature parasites, larvæ,
or eggs into the intestinal tract through the medium of food and drink
or by unclean fingers. This is particularly true of those parasites whose
habitat is in the intestine or other tissues within the body; such para-
sites are designated *Entozoa*. Parasites living in the outer tissues, as
the skin, are termed *Epizoa;* they remain on the surface of the skin or
penetrate into the deeper structures from without. The animal para-
sites for the greater part produce local changes, but can also cause symp-
toms of general disease, particularly when they increase in the body,
or produce toxic substances.

Many of the **parasitic protozoa** are harmless. Other forms, on the
contrary, penetrate into living tissues, increase within the cells,
and give rise to morbid changes, characterized by new-formations of
tissue (coccidia-disease of the rabbit's liver, epithelioma contagiosum).
Still other forms which are probably to be classed as Sporozoa, increase
in the blood, and destroy the red cells. Others (trypanosomata) inhabit
the blood-plasma. It is not impossible that such infectious diseases as
small-pox are caused by parasites belonging to the Protozoa.

The **parasitic worms** (*Nematodes, Cestodes, Trematodes*) occur in
man, partly in the adult and fully developed sexual state, and partly
in the larval state. Most of the adult worms are intestinal parasites,
and obtain nourishment from the intestinal contents, rarely sucking the
blood from the mucosa. Fully developed worms, however, are found
in other reigions, as in the blood- and lymph-vessels, bile passages, lung,
pelvis of the kidney, and in the skin. The eggs or fully developed
larvæ produced in the body by parasitic worms are either cast out with
the dejecta or, by wandering through the blood or lymph, reach other
organs, where they pass the first stage of their development. Here
they remain, however, in a larval condition, and do not reach sexual ma-
turity. The larvæ are capable of further development only when they
have been taken into a new host, or have been again eaten by the same
host.

Those worms which reach sexual maturity in the human body are
taken in as larvæ through the food and drink. Their first stage of de-
velopment is passed in the majority of cases in animals whose flesh
is used for food; in other cases in certain lower animals not used as
food. Others develop in water or damp earth or even in the human
intestine, so that the embryos or eggs, which pass off with the dejecta,
develop at once if they are again introduced into the intestinal tract of
man.

Worms which occur in man in the larval condition only (hydatids)
develop from eggs which have come from sexually mature worms, in-
habiting different animals. They are taken into the intestinal tract usu-
ally in the food or drink, but under special conditions eggs capable of
development may be contained in the dust of the air, and, being inhaled
and finally reaching the intestinal tract, complete the first stage of de-
velopment.

The intestinal parasites in most instances produce only slight me-
chanical irritation of the intestine. The presence of blood-sucking
worms, on the other hand (notably Anchylostoma duodenale and Un-

cinaria), are frequently productive of extremely severe anemia by the mechanical withdrawal of small quantities of blood for a prolonged period. Still other intestinal parasites manufacture poisons which are absorbed by the host. Thus Schaumann and others have demonstrated hæmolytic substances in the segments of Bothriocephalus latus, whose presence in the human body is sometimes associated with anemia of the pernicious type.

Those parasites which enter the tissues may cause in the vicinity mild inflammation and proliferation, producing marked clinical symptoms when the number of the parasites (*trichina larvæ*) is great. Others are of pathological importance, in that they reach large size (*echinococcus cysts*) and compress the neighboring structures. A parasite situated in the muscles or subcutaneous tissue may cause slight symptoms, while one in the eye, medulla oblongata, heart, or blood-vessels may cause severe disturbances, and under certain conditions death.

The **parasitic arthropoda** (*Arachnida* and *Insects*) come to the human body from the outer world, and from infected animals and human beings. They belong almost wholly to the Epizoa, which have their habitat in and on the skin and accessible mucous membranes (lice, bedbugs, fleas, mites) or occasionally take their nourishment from the skin (gnats, gad-flies, flies) ; a few multiply in the skin (itch-mite) or on its surface (lice). Flies and gad-flies occasionally lay their eggs on the mucous membranes or in wounds, and from the eggs so laid larvæ develop. The larva of an arachnoid (*Pentastoma denticulatum*) is alone found in the internal organs. When these parasites penetrate into the tissues, they cause irritation and inflammation; the bite of insects that suck blood is also followed by inflammation in the neighborhood of the puncture.

Attention has been directed to the fact that mosquitoes, stinging flies, gad-flies, bed-bugs, lice, etc., may be the **conveyers of infection,** in that bacteria or protozoa may be attached to their bodies, or that in the act of sucking blood of an infected man or animal they may take into their bodies bacteria or protozoa and convey them to other individuals. So far as experience goes, the danger of such conveyal is not great in the majority of the infectious diseases, since the bacteria thus taken up die after a time. This method of conveyal is of great importance, however, in **malaria,** in that the *plasmodia* taken from the blood of infected individuals by mosquitoes (anopheles) *undergo development in the body of the mosquito and produce a new generation, which through the bite of the mosquito is transferred to another individual.* Similar conditions exist in the case of the tsetse-fly disease and Texas fever of cattle, the latter being conveyed by ticks. Further, it is claimed by Manson, Sonsino, and others that the infection of man with filaria is also brought about through the agency of mosquitoes.

Of the parasitic protozoa there should be mentioned also the *Amœba dysenteriæ,* the cause of one form of dysentery in man; the *Trypanosoma evansi,* the cause of surra; *Tr. brucei,* the cause of the tsetse-fly disease or nagana; *Tr. gambiense* the etiological agent in human trypanosomiasis or sleeping-sickness; and the *Trichomonas* as a probable causal agent in catarrhal conditions of intestine or genito-urinary tract. Supposed protozoan parasites have also been described as the causal factors of smallpox, scarlatina, tumors, etc., but convincing proofs are not at hand.

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II.   Congenital and Inheritable Foundations for Disease.

1.   *Immunity, Predisposition, and Idiosyncrasy.*

§ 14. Toward the injurious agents capable of producing disease different individuals show different powers of resistance. Such differences are exhibited particularly in the case of the infections and poisons. When an individual is not susceptible to a given infection or poison, the property thus manifested is designated *immunity* and *insusceptibility;* but if an individual is easily infected by a pathogenic microörganism, we assume that he possesses a *predisposition* to the disease caused by the microörganism in question. Hypersusceptibility to influences having no effect on ordinary individuals is designated idiosyncrasy, and has particular reference to poisons, pollens, etc.

Immunity and *predisposition* represent the opposite behavior of an organism to external injurious agents, but they cannot be sharply separated from each other. In many cases immunity is not absolute but relative, so that an individual may be made ill through a given agent, for example, a pathogenic microörganism or poison, when the agent acts in its characteristic manner and strength. On the other hand predisposition may be so slight that disease arises only in extraordinary circumstances.

An *absolute immunity* or *insusceptibility* is possessed by man against many of the microörganisms pathogenic for animals, for example, against the bacteria of swine plague, swine erysipelas, and symptomatic anthrax. This may rest on the fact that the character of his tissue and tissue juices does not permit localization and multiplication of the causative bacteria, or that the poisons produced by the latter are not toxic for man.

The human race is *highly susceptible* to 'smallpox, measles, and influenza, so that many individuals acquire these diseases. In the case of scarlet fever, typhoid fever, diphtheria, the *susceptibility seems less*, but it is not possible to determine to what extent individuals who escape are not exposed to infection.

3

In many infectious diseases greater susceptibility is shown in childhood than in old age; for example, in diphtheria, whooping-cough, and scarlet fever. There are also variations in the degree of susceptibility at different times; for example, an individual may be exposed to measles without becoming infected, while at other times under apparently similar conditions he contracts the disease.

In the case of many pathogenic organisms there appears to be necessary for the occurrence of infection a certain *favoring condition or temporary increase of susceptibility.* As evidence of this is the fact that in the human alimentary canal, especially in the mouth and throat, as well as in the respiratory tract, pathogenic organisms (streptococci, staphylococci, pneumococci), may be present without any indications of infection. It may also happen that cholera spirilla increase abundantly in the intestine without symptoms.

Such occurrences may be explained by decrease or loss of virulence on the part of the bacteria, but this cannot be applied to all cases. In many instances it must be assumed that the harmlessness of the bacteria is due to the ability of the tissues to hinder their entrance into and their action on the deeper parts. In some cases this may depend on the structure and organization of the tissue, in other cases chemical substances have a determining influence (see § 29). In favor of the first assumption is the fact that tissue-lesions permit the entrance of bacteria, and promote infection. A *wound, therefore, in whatever way produced, forms a local predisposition,* and the disease, in such cases, bears the character of a **wound infection.** Infections caused by pus-cocci, tetanus bacilli, glanders, and anthrax bacilli are of this character.

Other causes leading to increased predisposition to infection are less easily recognized. It appears that severe *chilling, " taking of cold,"* or *hunger* may have this effect; also *changes in tissues due to preceding infectious or non-infectious local or general diseases* (see § 11, Secondary Infections). In the case of intestinal infections (typhoid, cholera), *gastro-intestinal disturbances,* play a rôle. Not infrequently it is impossible to determine what causes have favored the production of an infection at a given time.

Predisposition or **lessened resistance** is not infrequently shown to injurious agents other than those of infectious nature. Certain individuals are less able than others to withstand high temperatures, particularly if at the same time bodily labor is performed. Of soldiers on the march only a fraction may suffer from heat-stroke, although all are under the same conditions. The altitude at which different individuals become sensitive to the deficiency of oxygen, varies greatly. The effects of chloroform anæsthesia differ in different individuals. Many persons become exhausted through physical or mental labor at a time when in other individuals, under like conditions, no trace of exhaustion is discoverable; such influences operating daily in cases of special predisposition, may lead to disease.

Occasionally individuals show a degree of sensitiveness to external influences, which is anomalous to that usually observed, so that symptoms of disease arise which ordinarily would not affect the majority of mankind. Such sensitiveness is designated **idiosyncrasy.** It is exhibited particularly to certain chemical substances, in that articles of food or drink regarded as harmless act on such persons as poisons—eating of fresh fruit or sugar or salad produces nausea and vomiting. Others have

an aversion to dishes prepared from liver or kidneys, and become ill if they overcome this aversion and eat these foods. Still others, after eating lobster, strawberries, raspberries, morels, or asparagus, are affected with urticaria, a symptom characterized by an eruption of itching wheals. Certain persons are unable to drink boiled milk without unpleasant results. Alcohol, even in small doses, may cause marked excitation, or narcosis, or remarkable disturbances of the vaso-motor system. Doses of morphine or chloroform, which are borne by the majority without injury, may cause in certain individuals severe symptoms or even death. Some individuals show a high degree of sensitiveness, on the part of the mucous membranes of the respiratory tract, to the pollen of certain grasses, so that during the hay-harvest the inhalation of pollen gives rise to a catarrhal condition of the nose and conjunctiva, often of the larynx, trachea, and bronchi, which in severe cases may be associated with asthma and fever. These conditions are known as *hay-fever, hay-asthma*, or as pollen-diseases. According to the investigations of Dunbar, pollen contains a substance that may be extracted, and which, when injected subcutaneously into those disposed to this disease, causes symptoms of intoxication. Disinfecting fluids, such as corrosive sublimate or carbolic acid, in solutions which are ordinarily borne without discomfort, may, when applied to the skin of certain individuals, cause not only local disturbances of sensation, but may excite dermatitis of widespread proportions.

The importance of natural predisposition and immunity in the origin of infectious diseases has not only been made evident by the study of epidemics among men and animals, but has received confirmation by experimental investigation. If, for example, a mixture of bacteria be injected into an animal, only a part of these develop and produce tissue-changes; the others die. If the same mixture be injected into an animal of different species, the bacteria which develop are not the same as those in the first case. Further, bacteria which, when inoculated into a certain species of mouse, invariably cause death, may, when inoculated into a mouse of different species, be without effect. Mice are susceptible to anthrax, rats are nearly immune. The poison of the so-called septicæmia of rabbits kills rabbits and mice; guinea-pigs and rats are immune to it, while sparrows and pigeons are susceptible. The spirilla of relapsing fever may be successfully inoculated only into apes. Gonorrhœa, syphilis, and leprosy cannot be successfully inoculated into any of the lower animals with the exception of apes.

In the case of *natural antitoxic immunity* the toxins that enter the organism remain as perfectly harmless material in the body, and only relatively late are split in the process of metabolism. In such cases the avidity between the toxin and the body cells, their receptors respectively, may be wanting or slight. When not entirely wanting, an increase of the dose may produce intoxication. Immunity against small doses may arise through anchoring of the poison (for example, tetanus poison) to tissue elements changes in which do not produce symptoms of disease; or antitoxins may be present which render the toxins inert.

Nurslings and older children are *more susceptible to certain infections* than adults; particularly in the case of whooping-cough, diphtheria, measles, scarlet fever and tuberculosis. In the intestine of nursing infants, bacilli, tubercle bacilli in particular, are easily taken into the lymph-vessels; the skin of infants offers less resistance to the entrance of pus-cocci than that of older individuals. Young dogs may be infected with anthrax while old ones cannot. In this connection it should be noted that the slight susceptibility or the immunity of many adults is conferred by attacks of such diseases during childhood.

In *later life,* hæmorrhage into and softening of the brain, cardiac degenerations, cancerous growths, and the formation of gall-stones are of frequent occurrence. The *predisposition in old age to certain diseases* depends in part on degenerative processes, associated with premature senility of the tissues; in part on the fact that certain influences, which the years bring with them, gradually accumulate, so that

finally the changes which they produce become so prominent that they lead to functional disturbances and recognizable morbid conditions. Moreover, it is to be remarked that many symptoms occurring in old age are those of secondary diseases, which become apparent after other tissue-changes have reached a certain degree. For example, senile hæmorrhages, senile gangrene, degenerations of the brain and heart are dependent on disease-processes occurring in the arteries.

The *predisposition of the sexes* to certain diseases depends, in the first place, on the structure and function of the sexual apparatus. Pregnancy and the puerperium offer a favorable field for many diseases, for example, infection.

Differences of predisposition of different races are shown particularly in regard to malaria and dysentery, toward which the negro in general shows less susceptibility than the European. Malarial parasites may be present in the blood of the former without giving rise to symptoms of disease.

2. *Inheritable Diseases Based on Congenital Defects.*

§ 15. Among the **morbid conditions arising from congenital defects** and which appear spontaneously or are developed through external influences, there may be distinguished several groups; one in which the body as a whole is involved; another in which only part of the body is affected; and a third in which only a part of an organ presents changes of a pathological nature. There is no sharp dividing line between these groups. It is often impossible to determine what part congenital defects and what part extrinsic causes have taken in the production of such pathological conditions.

Among the **constitutional conditions arising from intrinsic causes** are to be mentioned the **development of dwarfs** and **giants.** The first is marked by under-development of all parts of the body, both the skeleton and soft tissues, while the second is characterized by growth exceeding that of the ordinary individual. It cannot be doubted that both dwarfism and giantism are dependent on congenital defects in the fetal architecture, but it cannot always be told to what extent such abnormalities in bodily growth are traceable to foundational faults or to pathological influences exerted during the period of development, such, for example, as disease of the thyroid gland, or of the pituitary.

Another constitutional peculiarity is **corpulence** (*obesity, adipositas, lipomatosis universalis*), in which fat is deposited in excessive amount either in tissues normally containing fat, or in regions which normally contain none, for example, beneath the endocardium or between the muscles. The increased deposit of fat is to be referred to disproportion between the production or supply of fat, and its consumption, pathological increase being at one time dependent on abnormal fat-production, at another on decreased consumption. Experience teaches that the energy with which metabolism goes on in the body varies at different periods of life, so that the normal amount of nourishment tends at one time to fatten, while at another time it does not.

In the pathological condition termed obesity, which in part at least is attributable to a congenital tendency, the energy of destructive metamorphosis is so altered that an abnormal amount of fat is deposited, even when a moderate or decreased amount is supplied.

Gout, like obesity, is a constitutional disease, which is partly dependent on congenital peculiarities, and at the same time is favored by intrinsic causes. The exact nature of the disease is not known. According to Garrod and Ebstein, the acute attacks of gout are caused by an accumulation of uric acid. On the other hand Pfeiffer holds that the essential feature of gout consists in the fact that the uric acid is pro-

duced in a form which is soluble only with difficulty. According to von Noorden, the formation and deposit of uric acid is a secondary process, induced by the presence of a ferment having a local action, and is consequently not dependent on the amount of uric acid formed in other parts of the body.

Pathological changes arising in single systems and organs on a congenital basis, may occur in any part of the body, and may involve an entire system or organ, or only part of one.

In the **skeleton** there may occur abnormal development of single parts, as, for example, smallness of the extremities (micromelia) or of the head (microcephalus) in contrast to the size of the trunk; overdevelopment of a bone or group of bones (macrocephalus, macrodactylism, giant growth of a finger, entire foot, or of an extremity); malformations of the extremities (cleft-hand, cleft-foot, etc.). Occasionally supernumerary bones, as carpal bones or phalanges, may develop, or atypical formations, such as bony outgrowths (exostoses, hyperostoses), which may extend over the skeleton to a greater or less extent, originating either spontaneously or following traumatism.

In the **muscular system** pathological bony formations are sometimes seen, notably in the condition known as myositis ossificans, which is apt to lead to progressive stiffness through the transformation of muscles into bony plates.

In the **vascular system** there occur either gross anatomical changes, such as abnormal branching of the arteries or mal-development of the heart; or finer changes, which reveal themselves through hæmorrhages (*hæmophilia*) the severity of which is out of all proportion to the injury, e. g., in such subjects the withdrawal of a tooth may be followed by long and almost uncontrollable loss of blood.

During the development of the **central nervous system** changes may occur which manifest themselves as *disturbance of function* or *as a special predisposition to disease.* Others are distinguished by *gross anatomical changes,* such as abnormal smallness of the brain (micrencephalon) or of the spinal cord (micromyelia), defective development or absence of particular parts (see chapter on malformations), misplacement of the gray matter (heterotopia), abnormal formation of cavities (syringomyelia), or abnormal formations of neuroglia. These may involve the functions of the sensory organs and the motor centres, and even the psychical processes.

Such conditions as idiocy and epilepsy have their origin in congenital predisposition. The tendency to crime has been ascribed to congenital predisposition, and Lombroso, in particular, has endeavored to prove that the man who lives through and for crime, the *Homo delinquens,* is a congenital criminal — that is, a man who possesses other physical and psychical characters than the normal in that he presents well defined stigmata of degeneration. According to Lombroso, subnormal development of the anterior half of the cranium, associated with corresponding lack of development of the anterior portion of the cerebrum, in connection with over-development of the posterior portion, produces feebler development of intelligence and of the moral sense, and favors the instinct-life. Benedikt goes so far as to maintain that the criminal possesses a peculiar configuration of the cerebral convolutions, similar in type to those of beasts of prey.

The views of Lombroso and Benedikt have met with much opposition. There can be no doubt that there does exist a degenerate species of the human race, which is characterized by such anatomical peculiarities as make it possible to distinguish a class of *Homo delinquens* from that of *Homo sapiens*. All the somatic peculiarities regarded as characteristic of the criminal, for example, the beast-of-prey type of cerebral convolutions, slightly developed frontal brain, receding forehead, massiveness of the lower jaw, asymmetry of the cranium, marked prominence of the arcus superficialis and arcus frontalis, pathological conformations of the skull, etc.— while relatively frequent in criminals, are far from infrequent in others. On the other hand, it is not to be doubted that the tendency to crime is frequently dependent on a congenital predisposition having its seat in some irregularity in the organization of the central nervous system. In this respect the criminal resembles the insane individual.

Pathological cerebral functions may develop in individuals of morbid predisposition without the occurrence of external injury, either during the period of development and growth or later. On the other hand such influences as over-work, sorrow, care, contribute to mental illness. In these cases the inherited tendency consists in a predisposition to mental disease so that influences which would produce no recognizable effects in a normal individual are sufficient to excite morbid phenomena. Since many influences, as diseases and infection, are adequate under certain conditions to produce mental disturbances in individuals who must be regarded as normal, it is difficult and often impossible to determine what part intrinsic and what part extrinsic causes have had.

Among the **congenital pathological conditions of the visual apparatus** are dyschromatopsia and achromatopsia, congenital partial or total color-blindness, which are frequently spoken of as Daltonism, and are characterized by want of perception for certain colors (most frequently red and green) or for all the colors. In this category belongs a variety of degeneration of the retina, in which there occurs a peculiar spotted, black pigmentation, associated with diminution of central vision and light-perception, with narrowing of the visual field. Finally, certain forms of myopia and albinism (absence of pigment in the choroid), are to be considered in this connection.

Of intrinsic conditions of the **auditory apparatus** deaf-mutism is of chief importance; this condition, in part at least, is dependent on disturbances of development. Further, certain malformations of the external ear fall into this class.

In the **skin** and **subcutaneous connective tissue** new-growths may develop on a congenital basis in the form of proliferations of connective tissue, at other times of epithelium. They often involve particular parts of the skin, as the nerves, blood-vessels, lymph-vessels, or the adipose tissue. When occurring as extensive thickenings of the skin and subcutaneous tissue, they constitute the foundations of the conditions known as fibromatous, neuromatous, hæmangiomatous, lymphangiomatous, and lipomatous elephantiasis. As circumscribed growths they are known as birth-marks, fleshy moles, lentigines, and freckles. The epithelial hypertrophies give rise to those conditions designated fish-scale disease or ichthyosis, ichthyotic warts, and cutaneous horns.

In addition to the pathological conditions which have been mentioned, there are **malformations of the body** (see chapter on malformations) **or of internal organs** which must be regarded as primary — i.e., which are not produced by injurious influences exerted on the developing fœtus. Finally, many forms of **tumors** (see chapter on tumors) are to be placed in this class, particularly those which are found at birth or which develop during childhood.

§ 16. **The origin** of diseases in which extrinsic influences are either entirely absent during both intra- and extra-uterine life, or are of significance only as a source of irritation sufficient to excite into development pathological tendencies which are already present in the body — may be explained in two ways: *Either the pathological peculiarities of the individual concerned are inherited from the ancestors, or they are developed from the seed, i.e., from the individual sexual nuclei that have copulated or from the segmentation nucleus resulting from their union.*

The inheritance of pathological qualities is clearly shown by clinical observations, inasmuch as many of the diseases due to intrinsic causes which are cited in § 15 also appear as inheritable characteristics in certain families. In some cases these characteristics are transmitted from the parents to the children, in other cases the grandchild may exhibit pathological peculiarities of the grandparents, the parents themselves remaining exempt; in other cases the pathological peculiarity may be manifested in the collateral branches, as from uncle to nephew. Dwarfishness and giantism are pathological peculiarities which frequently characterize certain families. Six fingers, cleft-hand and cleft-foot, hare-lip, dextrocardia, birth-marks, multiple exostoses, fibromatosis of the nerves, and multiple neurofibromata may appear in families for successive generations.

Hæmophilia is an inheritable condition. It is ordinarily transmitted through the daughter to a male grandchild, the daughter not showing the disease. There may occur, however, direct transmission of hæmophilia from parents to children. Partial or total color-blindness also occurs as a family disease, especially affecting the male members, and like hæmophilia is transmitted through the female line, which does not suffer, to the male descendants. The typical pigment-degeneration of the retina, myopia, deaf-mutism, certain forms of progressive muscular atrophy, and polyuria (Weyl) are also inheritable.

According to Gairdner and Garrod, in about ninety per cent of all cases of gout there is a family history of the disease.

Of the pathological conditions of the nervous system many are inheritable; to these belong periodic and circular insanity, epilepsy, hysteria, and to a somewhat less extent melancholia, mania, and alcoholism. Progressive paralysis, the deliriums, and conditions of nervous exhaustion are but slightly influenced by heredity (Kraepelin). Hagen estimates the number of hereditary insane at 28.9 per cent, Liedesdorf at 25 per cent, Tigges at over 40 per cent of all cases, while Forel holds that 69–85 per cent have hereditary taint.

In the more severe forms of transmissible degeneration the pathological condition itself is inherited. More frequently the predisposition is alone inherited and the morbid condition itself is developed later through the action of extrinsic influences on the central nervous system. The character of the disease in the descendants may be the same as in the

ancestors (*identical heredity*). More often the character of the disease is changed (*transformational heredity*), not infrequently in the sense that the severity of the condition increases from generation to generation (*degenerative heredity*).

According to Morel, there may appear, for example, in the first generation, nervous temperament, moral depravity, excesses; in the second, a tendency to apoplexy, severe neuroses, alcoholism; in the third, psychical disturbances, suicidal tendency, intellectual incapacity; in the fourth, idiocy, malformations, and arrests of development.

The occurrence of **inheritable diseases** is comparable to the well-known fact that in a family not only the peculiarities of race, but also of that particular family are inherited, and that often the qualities of either parent or of both recur in the children. As a hypothesis for the explanation of heredity, it is only necessary to assume that the peculiar quality under consideration represents not merely a somatic change accidentally acquired during the life of the ancestor, but rather a quality of the ancestor developed on a **congenital basis.** Diseases which in a normal individual arise only under the influence of some external injurious agency are never in a true sense inherited (compare § 17), but only those *pathological conditions existing in the germ* are to be regarded as examples of true inheritance. If a certain disease, as, for example, mental disease or myopia, is the product of a special inherited predisposition plus the effect of injurious influences which have acted on the body during life, only that part can be transmitted which has its seat in some peculiar congenital arrangement, but not that caused by external influences — the acquired condition cannot be inherited.

In *direct inheritance* — i.e., in that form of inheritance in which parental qualities are transmitted to the child — the transmission of normal as well as of pathological qualities is possible only when both sexual cells, in the condition in which they combine, contain the potential characteristics of both parents, in so far as these are transmissible. The product of the union of the sexual cells — the segmentation-cell — must, therefore, contain within itself both the paternal and maternal qualities. Since the sexual cells do not represent a product of the body developing during the course of life, but are rather to be regarded as independent structures, which at an early period of development are separated from the other parts of the body (that is, from the somatic cells) into special organs, where, protected and nourished by the body to which they belong, they lead an independent existence; the only possible explanation for the phenomenon of inheritance is found in the hypothesis that the ididual sexual cells contain, from the time of their origin onward, the potentialities which appear in the body in which they dwell. Both the sexual cells and the body itself, therefore, inherit in general the same qualities from the ancestors. Since in the act of frutification only the nuclei of the sexual cells — that is, parts of the same — come to copulation, we are compelled to assume that the nuclei are the bearers of inheritable qualities, and the peculiarities of the individual arising from the combination of sexual nuclei have their foundation in the organization of the nuclei.

The appearance in the descendants of normal or pathological characters belonging to the collateral relatives (uncle, great-aunt, or cousin), but which are not present in the parents, is known as *collateral inheritance.* This phenomenon is explained by the hypothesis that the sexual cells, in their origin, received characteristics which the bodies of the

parents did not receive, or which, at least, did not undergo development or were submerged in the parental bodies, whereas in certain relatives they did develop and become manifest.

The appearance in an individual of normal or pathological characteristics which were wanting in the parents, but were present in the grandparents or great-grandparents, is known as *atavistic inheritance*. This phenomenon is explained by the hypothesis that given characteristics of the grandparents or great-grandparents were transmitted to the sexual cells of the son, or of the son and grandson, without developing in the body of the first, while the quality thus remaining latent was re-awakened in the grandson or great-grandson.

The attempt has been made to give to the atavistic mode of transmission — which is of frequent occurrence and is usually confined to the immediate generations of ancestors — a wider significance in pathology. Thus it has been proposed to explain the occurrence of many newly arising pathological conditions, which appear similar to certain somatic qualities possessed by remote animal species in the ancestry of man, as a reversion to the type of these ancestors. For example, microcephalus and micrencephalus have been explained as a reversion to the ape type; and Lombroso is inclined to regard the *homo delinquens* as an atavistic phenomenon. There can be no doubt that certain writers have gone too far in this respect and have mistaken certain acquired pathological formations or new germ-variations (compare § 17) for atavistic conditions. Aside from the question of reversion to the type of the nearest generations of ancestors, atavism plays but an insignificant part in pathology, and it can really be employed only in the explanation of pathological formations in which the tissues show a certain fluctuation of behavior, so that not rarely formations arise which in phylogeny or ontogeny represent stages of the then normal conditions. In this category belong, for example, the occurrence of certain forms of the ear, supernumerary ribs, nipples, or mammary glands, and the development of certain muscles which are found in the closely related mammals.

It is held by many writers that *in individual cases, acquired pathological conditions may, under certain circumstances,* be transmitted *to the descendants.* Some even affirm hereditary transmission of deformities caused by injury. In support of their view they refer to the hereditary transmission of birth-marks, malformations of the fingers, myopia, mental diseases, predisposition to tuberculosis, etc., as examples which appeared in the first instance as acquired, and were then transmitted to the descendants. Further, they hold that they can point to observations on animals as giving evidence that injuries may cause deformities which are later transmitted to the offspring.

An unprejudiced examination, however, of the material collected in support of this view shows that *the hereditary transmission of acquired pathological characteristics does not occur.* The alleged proofs are found in part to be based on inaccurate observations, in part on incorrect inferences drawn from accurate observations. For example, the assumption that the occurrence of a birth-mark in a child in the same region of the skin as that in which the mother has a scar is proof of inherited deformity is wrong, inasmuch as birthmarks and scars represent two entirely different pathological processes. If, among the descendants of a man who suffered from some form of mental disease and who showed this disease only after a certain age, there appears an inheritable disease of the central nervous system, or if we note a similar occurrence in the case of myopia, we cannot conclude from such observations that the disease of the ancestor was an acquired condition. The term *acquired*, in the biological sense, can be applied only to that which in the course of the life of an individual arises exclusively from extrinsic influences, but not to a quality, the basis of which existed in the germ-cell, although this quality did not become manifest until excited by extrinsic influences. Should there appear in a

family inheritable mental diseases or hereditary myopia, the first case of such diseases may have been due to some pathological alteration of the germ, although no manifestations of the disease occurred until some of the outside influences of life excited it to activity, and so rendered possible the recognition of the pathological condition. The pathological condition in this case cannot, therefore, be regarded as acquired.

As opposed to the theory of the inheritance of acquired pathological conditions is the consideration that the human race, which is exposed to so many injurious influences, and whose individual members suffer so frequently from disease and mutilations, would soon deteriorate and eventually perish were only a small part of the acquired diseases transmitted to descendants. Further, the reproduction of man and animal forms through germinal cells is in itself an argument against the transmission of qualities accidentally or incidentally acquired by the individual.

Darwin represented the view that acquired characteristics could be transmitted to the descendants, and endeavored to make it intelligible on the theory that molecules from all the cells of the body contribute to the formation of the germ-cells, and that, consequently, alterations of the organism can be transmitted to the germ-cell. Nevertheless, there occur in the writings of *Darwin* statements which not only do not agree with this opinion, but contradict it.

The act of fructification—that is, the first step leading to the production of a new individual—is accomplished by copulation of the sexual nuclei—that is, of the nuclei of the ovum and spermatozoön. According to the researches of the last decades, there can be no doubt that *these nuclei are the bearers of the hereditary characteristics of the parents,* and that the individuality of the copulating nuclei is inherent in the organization of the same. It is impossible to conceive in what manner processes taking place in the body cells can produce in the sexual nuclei, which lie within special cells in the sexual glands, such alterations of organization that they shall contain in potential form the acquired characteristics of the body and transmit them, after copulation has occurred, to the descendants.

At the present time the views with regard to the inheritance of disease generally accepted are that there is no true inheritance of infections and that gross structural disturbances cannot be inherited. The only possible inheritance of conditions acquired by the parents is that of conditions acting both on the somatic tissues and germ-cells of the parents. Chemical and physical conditions acting within the body or from without may cause changes in the constitution of somatic and germ-cells. The occurrence of such changes in the germ-cells is clearly shown in the effects on the progeny of paternal or maternal alcholism, plumbism, and experimentally with abrin. It is a well-known fact that in the production of monsters there is often obtainable a history of some infection in one of the parents before conception took place. Bardeen's experiments regarding the changes in embryos arising from ova fertilized by spermatozoa that had been injured by Roentgen irradiation are very suggestive.

Recently much discussion has been waged over the principles of heredity involved in *Mendel's law, Galton's law,* and De Vries' *theory of mutations* (see literature).

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  See also § 15 and § 17.

§ 17. As has been explained in § 16, *inherited diseases are such as have developed from intrinsic causes, that is, from certain peculiarities in the germ-cells; or at least are diseases in which the predisposition thereto is a congenital characteristic.* Conversely, the statement may be made *that all normal or pathological qualities in the germ-cells are inheritable.*

The **appearance of new pathological characteristics which are inheritable** may be dependent on the fact that as a result of the union of two sexual nuclei, one of which is the bearer of the transmissible qualities of the father, the other of those of the mother — **variations** are constantly arising, so that the child is never exactly like one parent; but, in addition to the qualities which the parents offer, it possesses new qualities. Even if we assume that the sexual nuclei at times contain in potential form exactly the same characteristics as those of the parents, the product resulting from the union of these nuclei would present a certain degree of variation. However, the differences between the children of such parents would be but slight. As a matter of fact, different products of the same parents may show an infinite variety, by reason of the fact that the germ-cells themselves contain a mixture of the transmissible characteristics of the paternal and maternal ancestors, and this mixture is never the same.

In accord with this is the fact that the children of a certain family always present important differences in both physical and mental qualities. A marked resemblance occurs only in the case of twins arising from one egg — i.e., when the process of development of both children has started from the same act of copulation.

The **embryonal variations resulting from the mixture of two individually different hereditary tendencies** find their expression in varied qualities of body and mind of the developing child. If these do not deviate in marked degree from the characteristics which other members of the family show, the conditions are regarded as normal and ordinarily receive no special attention. If, on the contrary, important differences are produced, the fact attracts attention; and, according to the value which it has for the individual concerned, is regarded at one time as something favorable, at another time as something unfavorable, something pathological. When small, weak parents produce children who develop into large and strong individuals, or when the intellectual capacity of the children surpasses that of the parents, the occurrence is regarded as favorable. If, as happens, a genius suddenly appears in a family, without any evidence of extraordinary mental development in the ancestors, the phenomenon attracts attention and is regarded as a fortunate event. But if, on the other hand, strong parents beget children who are weak or defective, or if they show a mental development inferior to that of their parents, or stunting of their mental faculties, *the newly appearing variation is regarded as abnormal, pathological.*

The assumption seems warranted that of **transmissible pathological conditions and predispositions,** many, perhaps the majority, **are referable to a variation of the germ based on the amphimixis..** For example, the group of hereditary pathological conditions and predispositions of the central nervous system, hereditary myopia, hæmophilia, pigmentation of the retina, and polydactylism may arise in this manner. If such abnormal characteristics show themselves repeatedly in the children of parents who are themselves normal and have healthy ancestors, it may

be assumed that the germ-cells of the parents, though individually normal, have through their union given rise to pathological variation. This hypothesis becomes substantiated when one or both parents produce normal offspring through copulation with other individuals.

Besides those variations which are the result of normal sexual reproduction, it is probable that pathological germ-variations which lead to the development of transmissible pathological qualities may also arise through the action of **injurious influences on the sexual nuclei or the segmentation nucleus**; or that the union of the sexual nuclei **has been disturbed.** The injurious substance may be a body-product, or it may come from without, and at the same time produce its harmful effects. Consequently, in these cases we may speak of the **germinal acquisition** *of a transmissible pathological characteristic through the action of an extrinsic injurious influence.* This does not mean, however, as has been accepted by many, that the tissues of the body, under the influence of extrinsic harmful influences, suffer changes in themselves, and then transfer these changes to the germ-cells. It is to be believed, rather, that the harmful influence acts directly on the sexual nuclei or on the segmentation-nucleus, producing in these a *change* which later leads to pathological development in the individual developing from the impregnated egg. It is a matter of no importance, so far as the nature of the resulting pathological variation is concerned, whether the somatic tissues also suffer changes, or what the character of these may be.

If a transmissible pathological characteristic arise, it may, if it does not affect life or prevent reproduction, be transmitted, although this does not necessarily follow. The chances that a particular characteristic will be transmitted are greatest when both parents possess the same quality, as, for example, when both parents are affected with hereditary deaf-mutism or with near-sightedness. If the characteristic is wanting in one parent, there is produced most frequently a new germ-variation, in which the pathological characteristic fails entirely to manifest itself, and in following generations may completely disappear. If several descendants are begotten, the pathological characteristic, if it be not wholly lost, may show itself in only a few of the descendants, and in either modified or aggravated form. Not rarely it happens that the characteristic remains latent in one generation — that is, confined to the sexual cells, and appears again in the second.

§ 18. Besides the inheritable pathological conditions mentioned above, **hereditary transmission of infectious diseases sometimes occurs.** This is not a true form of inheritance, but is more properly designated as **postconceptional intra-uterine infection.**

If pathogenic micro-organisms enter the blood-stream of a pregnant woman they may be carried into the vessels of the maternal placenta, and may pass through the foetal placenta into the body of the foetus. Such transmission has been demonstrated in many infections (staphylococcus, streptococcus, pneumococcus, typhoid fever, anthrax, smallpox, syphilis, and others) through the presence of the micro-organisms or of characteristic changes in the tissues of the foetal organism. In certain cases, for example, in anthrax, the path which they have taken may be demonstrated since the placenta shows characteristic pathological changes.

It was once assumed that besides **placental transmission** there might also occur **germinal transmission,** that is, infection of the sexual cells before or during fructification. Further, it has been taken for

granted, that, through infection of the fructifying spermatosome, infection of the ovum without that of the maternal organism may occur, and such a mode of infection has been regarded as established, particularly in syphilis. Up to the present time, however, this mode of transmission has not been proved by unquestioned observations to occur in man and the mammals, and its occurrence even in syphilis has also been thrown into doubt (Matzenauer). According to our present knowledge we may say definitely that the transmission of infections through the placenta to the fœtus *in utero* has been positively demonstrated and occurs in different infectious diseases. Infections of the ovum or of the sperm before or during fructification are indeed possible, but it has not yet been positively demonstrated in the case of man and the other mammals that a further development into a viable fœtus is possible in the case of an ovum in which the agents of infection have produced characteristic changes. This is true not only in the case of acute infections, but also in such chronic ones as tuberculosis and syphilis.

According to the views of *Matzenauer,* in no case of hereditary syphilis can maternal transmission be excluded; and there are no clinical observations that speak for a pure paternal spermatic infection of syphilis. The fact that the mothers of children showing hereditary lues are immune toward syphilis (Colles' law) cannot be explained by the hypothesis that the mother has received syphilis toxins from the child syphilized from the father and in consequence has produced antitoxins (*Finger*), but can be explained only on the ground that she herself was infected with syphilis. That the mother often shows no syphilitic changes cannot be taken as an argument against the latter view, since syphilis may often be present with complete absence of symptoms.

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CHAPTER II.

The Spread and Generalization of Disease Through the Body. Autointoxications and Secondary Diseases.

§ 19. **Primary local disease** is accompanied by disturbance of function of the affected part. If the causative agent passes into the lymph stream or blood without causing noticeable changes at the point of entrance, while within the body it gives rise to solitary or multiple foci, the disease thus resulting is designated **lymphogenous** or **hæmatogenous,** as the case may be.

Local diseases may remain confined to the organ originally affected; frequently they lead to **secondary diseases of organs** or to **general disease.**

One *method by which disease spreads* through the body is by the process of *metastasis,* by means of which not only solitary, but innumerable foci arise in different parts. Not infrequently *dissemination of disease* by the blood and lymph-channels (tuberculosis, suppuration, and malignant growths) may proceed to such an extent that the majority of the organs are thus secondarily involved.

A *second method* occurs in which at the primary focus toxic products are formed, and these, when taken into the lymph and blood, produce local changes due to the effects of poisoning. Such intoxication is of common occurrence in the *infectious diseases,* and leads not only to *secondary degeneration of organs,* but even to *general disease,* as shown by constitutional reactions characterized by disturbances of metabolism and fever.

A *third form* of the spread of disease through the body becomes possible by reason of the fact that the integrity and normal functional capacity of many organs are in great measure dependent on the function of other organs; and, further, on the fact that the organism needs, for the preservation of its normal condition, the perfect functional working of its organs. There is, therefore, a large group of *local and general diseases which arise as the result of the imperfect functional activity of individual organs.*

A *fourth mode* of origin of secondary diseases is through *autointoxi*cation — that is, through *poisoning of the organism by substances which arise in the body itself* (*metabolic poisons*). These substances may arise in the intestinal tract (*enterogenous poisons*), or in the tissues (*histogenous poisons*). The poisonous action of these products of metabolism lies partly in the fact that they are produced in increased amount or are retained in the body as a result of disease of certain glands; or because they are not transformed to non-poisonous bodies, as in normal circumstances. In conditions of disturbed metabolism poisons foreign to the normal body may be produced.

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A *fifth method* by which the body may be injured is through *loss of function of those glands producing an internal secretion.* In this category belong the thyroid, hypophysis, pancreas, adrenals, and sexual glands. Since in disease of the glands just named intoxication plays an important rôle, this group of processes is closely connected with that of the fourth mode of generalization of disease.

I. Metastasis and Embolism and their Significance in the Etiology of Lymphogenous and Hæmatogenous Diseases.

§ 20. *The transportation, through the blood or lymph-stream, of a disease-producing agent, and the production of disease at the point of deposit,* is termed **metastasis**. This is one of the common modes of the spread of disease through the body. Ordinarily the term metastasis is applied to those cases in which the transportation of a given substance is followed by easily recognizable clinical and anatomical manifestations of disease, especially those of inflammation or tumor-formation, so that we are accustomed to speak of *metastatic inflammations* and *metastatic tumors.* There is, however, no good reason for not including under metastasis those cases of transportation of corpuscular elements through the lymph or blood stream in which the changes produced by the transportation are less striking, and are recognizable only through careful anatomical or microscopical investigation.

Fig. 1.—Multiple emboli in the branches of the pulmonary artery, after thrombosis of the right auricle. *a,* Arterial branch; *b,* embolus; *c,* embolus with secondary thrombosis.

The term metastasis indicates that the substance deposited has arisen from some other place in the body, and we are accustomed to speak of **lymphogenous** or **hæmatogenous metastasis,** depending on the mode of transmission.

The **significance of metastasis** is **dependent on the properties of the transported body.** Insoluble bland foreign bodies of small size may have little effect on the tissue; soluble and chemically active substances may, on the other hand, produce important tissue changes. Bacteria capable of reproduction may give rise to disease which corresponds to that produced at the primary focus of infection. Tumor-cells may develop a secondary tumor. The **size** of the transported body is of importance in hæmatogenous metastasis, in that small bodies may pass all the blood-vessels, even the capillaries, while larger ones are carried only through those vessels whose lumen is sufficiently large to admit them. When the latter obtain entrance to the arteries and are carried along by the blood-stream, they become lodged at those divisions of the vessels where the lumen is too small to admit them, and more or less completely obstruct the lumen. This occurrence is designated **embolism;** the body blocking the vessel is the **embolus** (Fig 1). The effect of embolism is more or less complete obstruction of the vessel, partly through the presence of the embolus itself, partly through associated coagulation of the blood. As a result of such obstruction there is in-

terference with the circulation, which may vary greatly in different cases; behind the point of obstruction there may be established either complete or partial collateral circulation, in other cases such compensation may be wanting. When compensation is incomplete or absent, the tissue supplied by the obstructed vessel undergoes degeneration or dies.

Both lymphogenous and hæmatogenous metastasis usually occur in the direction of the normal current, but transportation in the opposite direction may take place—**retrograde metastasis.** Such a change of current in the lymph-vessels occurs when the escape of lymph from the region involved is hindered through stoppage of the lymphatics, and the lymph is forced to seek other outlets. A similar condition may occur in circumscribed areas supplied by the peripheral blood-vessels. In this way clots arising in the right heart or in the large veins of the body may be transported to the peripheral veins, particularly under conditions in which backward waves of blood gradually force the clots into the smaller veins. According to the investigations of Arnold on dogs, foreign bodies (wheaten grits), which were too large to pass the capillaries, when introduced into the jugular or crural veins, as well as into the longitudinal sinus of the dura mater, were carried by retrograde metastasis not only into the main trunks, but into the smallest branches of the veins of the liver, kidneys, heart, extremities, dura mater, pia mater, and orbit, and into the posterior bronchial veins.

In the case of a defect in the septum of the heart, bodies circulating in the blood may pass directly from one side of the heart to the other, and thereby give rise to **crossed** or **paradoxical embolism.**

§ 21. **The substances which are transported in the process of metastasis** may be divided into six groups, this classification being based partly on the origin and character of the transported body, and partly on the effects of its lodgment.

In the first group are placed insoluble lifeless substances composed of small particles, which enter the body from without, and may be designated collectively as **dust.** The majority of these substances enter the body in the respired air, and pass from the lungs into other tissues. Others enter the tisues through accidental or intentional wounds (tattoo). Most frequently these substances are particles of soot, coal- and stone-dust, more rarely metal, porcelain, tobacco, hair or other kinds of dust. In tattooing of the skin, lampblack, india-ink, ultramarine, and similar granular pigments are used.

The behavior of the tissues toward such substances will be treated of elsewhere; it is only necessary to mention here that these forms of dust, sometimes in a free state, sometimes enclosed within cells, are first deposited in the tissues nearest the point of entrance, later in the lymph-vessels and lymph nodes. In the latter location they may remain for a life-time; but in cases of excessive deposit they may be carried beyond the lymph nodes, especially in those instances in which the nodes, because of the great deposit, undergo softening and give rise to inflammation and proliferation of the tissues in the neighborhood. Often as a result of such changes the affected nodes become confluent with and break into neighboring veins. This event is especially likely to happen at the hilum of the lungs, whereby the contents of the node ultimately, sometimes slowly, at other times more rapidly, gain entrance to the vessel-lumen and are carried away by the blood-stream. In the lungs,

dust may be deposited directly in the vessel-walls and gradually pene-trate as far as the intima. Further, the particles from a broken-down lymph node can enter the lymph-stream, and, if not arrested by some other lymph node, may reach the blood-stream. It is also conceivable that softened lymph nodes may break directly into the thoracic duct. In fact, rupture of a tuberculous node into the receptaculum chyli is a recognized mode of origin for the rapid dissemination of tubercle bacilli through the body (acute miliary tuberculosis).

As numerous experiments have shown, dust gaining entrance to a blood-vessel remains but a short time in the circulation. Large amounts artificially introduced into a vein disappear in a few hours from the circulating blood. The greater part collects in the capillaries of the liver, spleen, and bone-marrow, partly free and partly within leucocytes, in the former case adhering to the surface of the endothelium. After a short time the leucocytes containing the dust particles wander out from
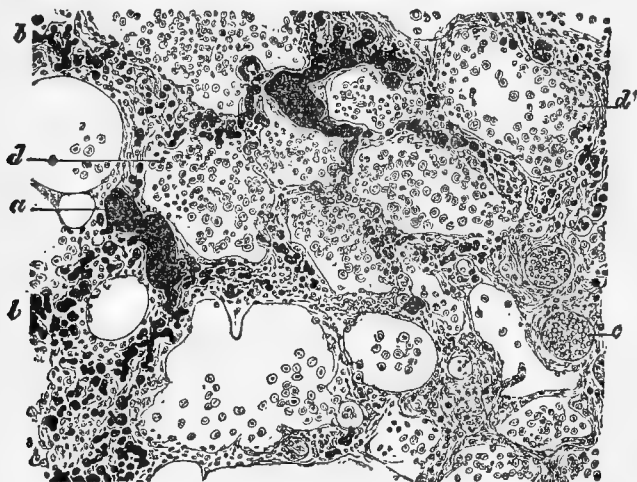
Fig. 2.—Fat-embolism of the lungs (Flemming's solution, safranin). a, Arteries filled with blackened masses of fat; b, fat-droplets in capillaries; c, veins; d, cells in the alveoli. × 100.

the vessels and the dust collects in the tissues, where it is held for a long time, in wandering or in fixed cells, or free. It may remain here during the lifetime of the individual, or be carried in the lymphatics to other regions and deposited, particularly in the portal and cœliac lymph nodes. According to the researches of Kunkel and Siebel, still other cells containing dust-particles may reach the surface of the body-cavities, either through the lungs, the parenchyma of the tonsils, and probably also from the lymphoid tissue of the intestines, and in this way be discharged externally. From the liver the dust-particles may be discharged in the bile. According to observations made on inflamed organs, wandering leucocytes are able to take up a great number of the particles lying in the tissues and transport them from the lungs, intestinal tract, and other organs to the surface, and in this way clear the tissues.

The second group is composed of portions of the body itself, namely, **tissue-detritus, parenchyma cells, and dead, coagulated, and broken-up constituents of the blood.** Of the elements arising from the destruction

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of tissue, **fat-droplets** (Fig. 2, *a, b,* and Fig. 3, *a, b*) often find their way into the circulation; particularly when through trauma or some other pathological process, as, for example, hæmorrhage, the tissues are destroyed. This occurs most frequently in cases of crushing, destruction, and violent agitation of fat-tissue, as may happen in the different panniculi adiposi and the bone-marrow; fat may also enter the circulating blood through destruction of liver-tissue. The parenchyma cells most frequently entering the circulation are *liver-cells, syncytial placenta-cells, portions of chorionic villi,* and *bone-marrow cells.* Ordinarily these are carried into the pulmonary arteries and capillaries, but through retrograde metastasis they may be carried into the veins, and through paradoxical embolism into the arteries and capillaries of the systemic circulation. Embolism of liver-cells and bone-marrow giant-cells is caused by traumatic and toxic injuries and hæmorrhages of the affected tissues. Placental-cell emboli, in the form of syncytial giant-cells, have been observed in puer-
peral eclampsia, but occur also in the course of normal pregnancies. Pulmonary emboli composed of small portions of the chorionic villi have been observed. In diseased conditions of the intima of the heart or blood-vessels, *degenerated endothelium, broken-down and degenerate masses of intima, portions of the valves,* and material of similar nature may gain entrance to the blood-stream. *Fragments of blood-corpusles* may enter the circulation from hæmorrhagic foci or may arise within the vessels them-

FIG. 3.—Fat-embolism of the kidney (Flemming's solution, safranin). *a,* Glomeruli with fat in the capillaries; *b,* fat-droplets in the intertubular capillaries. × 100.

selves, in degenerative changes produced in the blood through the influence of the various harmful agents. Coagulated *masses of blood* enter the circulation when a **thrombus**—i. e., blood coagulated in the vessels (see Chapter IV)—breaks loose, either *in toto* or in fragments.

The fate of the last-named substances is for the chief part dependent on their size and physical properties. All fragments of greater diameter than the lumen of the capillaries become lodged in the bifurcations of the arteries (Fig. 1, *a, b*) and usually occlude the same. This occurs most frequently in the case of dislodged thrombi or of fragments of such; on the other hand, fat-droplets usually pass into the capillaries, where part remain, while others pass through and become lodged in some other place. Since the fat occasionally passes first into the veins of the body and thence to the heart, the fat-droplets collect especially in the capillaries of the lungs (Fig. 2, *b*); but they may also pass through the lungs into the capillaries of the greater circulation, and are then found in the intertubular and glomerular capillaries of the kidneys (Fig. 3, *a, b*), and to some extent in the capillaries of other organs. Capillary fat-embolism causes noticeable disturbances of the circulation only when of extensive occurrence; in this case it may lead to the production of œdema of the lungs. Furthermore, the fat disappears in the progress of metabolism, or is conveyed into the neighboring tissues.

Parenchyma cells become lodged in the capillaries or smaller arteries in the case of arterial metastasis. The latter is especially true of liver-cells when entering the circulation *en masse*. At the place of lodgment their presence may lead to heaping-up of blood-plates and hyaline coagulation. The cells themselves do not multiply, but may remain unchanged for a time, according to Lubarsch, as long as three weeks. They then gradually die, the protoplasm dissolves, the nuclei swell or shrink, and finally lose their chromatin.

The point of lodgment of loosened thrombi or fragments of thrombi depends on the path which they take, as well as on their size. Since thrombi may be formed in the systemic veins, right heart, and pulmonary arteries, as well as in the pulmonary veins, left heart, and systemic arteries (see Chapter IV.), it is possible for embolism to occur in any of the arteries of the greater or lesser circulation. Often emboli lodge at the bifurcation of arteries, forming the so-called **riding** or **straddling emboli** (Fig. 1, *c*). Through retrograde metastasis emboli may be carried from the venæ cavæ or larger veins into the smaller veins. Defects in the septum of the heart may lead to the production of paradoxical embolism.

Small fragments of thrombi, dead red blood-cells or fragments of such, endothelial cells undergoing disintegration or fatty degeneration, etc., meet the same fate as dust-particles. They may remain free or be taken up by cells; but are soon removed from the circulation and collect in the spleen, liver, and bone-marrow, where they undergo further changes and are destroyed. The products resulting from the destruction of red blood-cells may persist for a long time in the organs named, as pigment deposits.

The third group of substances producing metastases is composed of **living cells,** which, originating from **proliferating tissue-foci** and having gained entrance to the circulation through rupture into the blood-vessels, or having entered the lymphatics, are carried to other organs. This process may be observed in the case of **tumors** growing by infiltration. The metastasis of living cells from a tumor leads through proliferation of the transported cells to the production of **metastatic secondary tumors,** which in lymphogenous metastasis develop first in the lymph-vessels and lymph nodes, but in the event of direct rupture into the blood-vessels arise in that part of the vascular system to which the tumor-cells are carried by the blood. The metastasis usually occurs in the normal direction of the blood- and lymph-streams, but *retrograde transportation* may occur, so that a tumor which has broken into one of the systemic veins may give rise to metastases in the region drained by smaller branches of other systemic veins. Retrograde metastasis is not infrequently observed in the lymphatic system, when closure of the efferent lymph-channels has produced a change in the direction of the lymph-current.

In the fourth group may be placed all those processes characterized by the entrance of **vegetable** or **animal parasites** into the circulation. If in such circumstances these organisms do not find conditions suitable for their development, they are eliminated from the blood-stream and destroyed. But if they are able to reproduce themselves, they give rise to **metastatic foci of infection,** partly in the vascular system, but also extending thence into neighboring tissues. The secondary foci produced by bacterial invasion have in general the same character as that of the

primary. If an embolus contains organisms capable of producing tissue-necrosis, inflammation, and putrid decomposition, repetition of the same processes will occur at the place of lodgment.

In the fifth group of metastatic processes may be classed those cases in which **constituents of the human body having undergone solution** are transported in the soluble state and **deposited in a solid form;** and also those in which **extrinsic substances are taken up by the body in a soluble form** and are **deposited in the tissues in a solid state.** Frequently bile-pigment enters the circulation within the liver, and permeates the tissues, giving to them a yellowish color (*icterus*). Not infrequently *iron-containing derivatives arising from the destruction of red blood-cells in the circulation* are carried to the spleen, bone-marrow, liver, and kidneys and form pathological deposits of iron (hæmatogenous siderosis). *Fat* can be split from the fat depôts in the form of soluble soaps and carried through the blood to different organs where it is taken up by the cells and changed into neutral fat.

When preparations of silver are, for medicinal purposes, introduced into the body through the gastro-intestinal tract for long periods of time, there may occur a deposit of fine *granules of silver* in the connective tissue of the skin, in the glomeruli, medullary pyramids of the kidneys, intima of the large arteries, adventitia of the small arteries, in the neighborhood of mucous glands, connective tissue of the intestinal villi, in the choroid plexus of the cerebral ventricles, and in the serous membranes. Tissues showing such a deposit have a grayish color.

The fact that epithelial tissues and the brain are not affected shows that there is a selective action on the part of the tissues, and that this selective action differs essentially from that which is seen in the metastatic deposit of corpuscular elements. It may be assumed that the chemico-physical character and the functional activity of the tissues coming into contact with substances in solution exert a determining influence on the separation and precipitation of such substances.

In a sixth group of metastatic processes may be classed the entrance of **air into the circulation.** If a large amount of **air gains entrance to the right heart,** an event which occurs especially in case of injury to the large veins lying in the neighborhood of the thoracic cavity, or more rarely from the opening of a vein, for example, in the stomach, through ulcerative processes, the air mingling with the blood forms a foamy mass, which the contractions of the heart are not able to drive onward. As a result the left heart receives little or no blood, the aortic pressure falls, and the individual quickly dies. Should the air enter the circulation in small amounts or intermittently, it may be carried by the blood-stream in the form of bubbles and circulate through the body. Larger amounts may lodge for a time in the vessels of the major or minor circulation, obstruct their lumen, and cause disturbances of the circulation, which give rise to functional disturbances of the brain and respiration. If these conditions do not cause death, the air is after a time absorbed.

If the lung-tissue be ruptured through trauma or violent coughing, screaming, or vomiting, etc., **air may be forced into the connective-tissue spaces and lymphatics,** and may extend through these into all parts of the lungs, pleuræ, and the mediastinum, as well as into the skin. The condition thus produced is termed *emphysema* of the skin, of the subcutaneous tissue, of the mediastinum, etc. In certain circum-

stances the air may spread through a large area of the subcutaneous lymph-vessels and connective-tissue spaces, and the skin presents an inflated appearance and when pressed upon produces a crackling sound.

According to *Siebel* and *Kunkel,* granules of cinnabar and indigo injected into the blood-stream of a frog are quickly taken up by leucocytes, and after one to two hours no free granules are to be found. After twenty-four hours the leucocytes containing pigment-granules have disappeared from the circulation, and lie clumped in the capillaries, the greatest number being found in the spleen, liver, bone-marrow, and lungs, while they occur in smaller numbers in the kidneys, and in still smaller numbers in the capillaries of the heart-muscle.

Even after two hours free pigment and cells containing granules are found outside the vessels, and after a few days they have almost wholly disappeared from the vessels. The granules lie partly in wandering-cells, partly in fixed cells, and in the free cells of the splenic pulp (*Ponfick*) and bone-marrow. They may be found in these organs for weeks afterward (*Hoffmann, Langerhans*). In both frogs and dogs some of the granule-containing cells find their way into the lumen of the alveoli and bronchioles and so pass out of the body. In the liver the pigment-particles adhere for a short time to the endothelium of the capillaries and may be taken up by the endothelial cells (*Browicz, Heinz*); another part is found in leucocytes, which later wander out from the vessels into the tissues. Thence they are in part taken up into the lymphatics of the liver and ultimately reach the lymph-nodes. A part of the granules finally passes out with the bile, but by what course they reach the bile-vessels is not known. In dogs the pigment-granules also collect in the tonsils and are carried to the surface through the epithelium by the leucocytes which have taken them up.

According to the observations of *Jadassohn* ("Pigmentverschleppung aus der Haut," *Arch. f. Derm.,* 24 Bd., 1892) and *Schmorl* ("Pigmentverschleppung aus der Haut," *Centralbl. f. allg.* Path., 4 Bd., 1893), both normal and pathological pigment may be transported from the skin to the lymph-nodes — in other words, *pigment-metastasis* takes place.

According to *Lewin* (*Arch. f. exp. Path.,* 40 Bd., 1897), if the outflow of urine from the bladder be hindered, small foreign bodies can pass into the kidney-pelves, and thence into the urinary tubules, lymph-vessels, and veins, and into the general circulation.

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II.   The Sequelæ of Local Organic Disease.

§ 22. **Secondary diseases** occur with great frequency as phenomena associated with *pathological changes in the blood and circulatory apparatus.*

The circulatory apparatus and the blood bear intimate relations to all the body-tissues, and accordingly *diminution in amount* and *pathological alterations* of the blood, *as well as changes in the blood-vessels,* often give rise to disease conditions. If the hæmoglobin-content of the blood is decreased through diminution in the number of red blood-cells (oligocythæmia), or through a pathological condition of the same, or if the hæmoglobin through the action of carbon monoxide is rendered incapable of taking up the oxygen of the air, the body-tissues no longer receive a normal amount of oxygen; consequently if the degree of oxygenation falls below a certain point, disturbances of nutrition arise, and are most frequently exhibited in the form of fatty degeneration of the heart, kidneys, liver, and other viscera.

Should *an artery become narrowed or closed through thrombosis or embolism, or thickening of its walls,* as in the disease known as *arteriosclerosis,* there arise in the region supplied by the affected vessel a local deficiency of food and oxygen, *local asphyxia,* and later *degenerative processes,* which frequently end in death of the specific parenchymatous elements, at times also of the connective-tissue framework.

In the brain and spinal cord the vessel-changes lead to ischæmic softening, which frequently results in paralysis, and not rarely in death. In the heart diffuse fatty degeneration or local softening of the heart-muscle may occur, giving rise to disturbances of cardiac activity or even to complete insufficiency. In the kidneys the secreting parenchyma, to-

gether with a portion of the connective tissue, undergoes necrosis or atrophy; and the loss of these substances gives rise to local or widespread contractions, which, according to their origin, are designated embolic or arteriosclerotic atrophies.

In the stomach ischæmia of the mucous membrane gives rise to local ulcerations; in the liver and muscles to atrophic conditions. No tissue can withstand the harmful effects of long-continued anæmia, and consequently the narrowing and closure of arteries, through the formation of clots or changes in the vessel-walls, play an extremely important rôle in pathology; and are not only the causes of *anæmic necrosis* (see Chapter V.) and *hæmorrhagic infarction* (see Chapter IV.), but also of numerous *progressive atrophies of organs.* In the pathogenesis of the last named, arteriosclerosis has an especially important part, since in old age it is of common occurrence, and gives rise to tissue-degenerations in organs of widely different structure. The majority of the affected organs show areas of scar-tissue, in which the specific parenchyma has disappeared while the connective tissue has increased.

The active participation of the vascular apparatus in all *inflammatory processes* (see Chapter VII.), the *disturbance of circulation* through alteration of the vessel-walls, the *shifting and changes in the vascular channels* which result from the *closure of vessels by proliferation of endothelium and connective tissue,* or through *thrombosis,* as well as from the *formation of new vessels,* make easily comprehensible the fact that in all chronic inflammations the specific cells dependent on regulated nutrition undergo degeneration and are frequently replaced by connective tissue of a lower grade than normal.

Profuse watery discharge from the *intestines* may deprive the body of water. If, as a result of stenosis of the œsophagus or pylorus, food is prevented from entering the intestinal tract, or if the stomach and intestine are no longer able to digest food and to prepare it for assimilation, the organism as a whole becomes poorer in albumin and fat.

If the *heart* is no longer able to propel with normal strength the blood coming to it, there arise in various organs changes due to venous stasis. If *respiration* is imperfect, the composition of the blood suffers. Collection of fluid in the thoracic cavity causes compression of the lungs; such mechanical interference may lead to atrophy. If a part of the *lung* has been rendered useless by chronic inflammation, the inspiratory enlargement of the thorax affects only that portion of the lung which is capable of functionating, and this part becomes over-distended and finally atrophic.

Disease of the parenchyma of the liver often gives rise to disturbances of the circulation of the blood through the organ, and stasis throughout the portal circulation with resulting ascites. Should the *pancreas* be destroyed or if it is no longer able to produce its ferments (proteolytic trypsin, amylolytic diastase, and the fat-splitting and emulsifying steapsin) there results imperfect metabolism of albumin, carbohydrates, and fat.

Hindrance to the outflow from the ureters reacts on the secretion of the kidneys and leads to atrophy. The loss of a *large portion of the renal parenchyma* is followed by increased blood-pressure in the aorta, increased action of the heart, and hypertrophy.

Increased resistance in the pulmonary circulation due to diseased conditions of the lungs is often followed by dilatation and hypertrophy of

the right heart. *Obstruction to the flow of blood through the aortic opening* is followed by hypertrophy of the left ventricle. Stenosis and insufficiency of the mitral valve cause a stasis of blood backward through the lungs to the right heart. This may be compensated for through hypertrophy of the right ventricle, or the process of stagnation may extend into the veins of the systemic circulation.

An *oblique position of the pelvis* leads to curvature of the spine. *Stiffness* and *immovability* of a joint cause atrophy of the muscles which normally control the movements of the joint, the atrophy being due to inactivity.

Diseases of the nervous system may give rise to functional disturbances and anatomical changes in any organ of the body—in glands, muscles, skin, bones, lung, heart, intestine, etc. Destruction of the ganglion-cells in the anterior horns of the spinal cord leads to atrophy of the corresponding peripheral nerves and muscles. Paralyzed extremities become atrophic. Injury to certain portions of the medulla oblongata, or the presence of tumors in the brain may be followed by or associated with withdrawal of the glycogen of the liver into the blood-stream and the excretion of sugar in the urine. Stimulation of peripheral nerves may produce abnormal reflex sensations and movements as well as circulatory disturbances in other parts of the body. Paralysis of both vagi or of their branches, or the recurrent laryngeal nerves, through inflammatory changes or pressure from enlarged lymph nodes, etc., may be followed by inflammation of the lungs, in that the accompanying paralysis of the laryngeal muscles favors the entrance of foreign bodies during inspiration.

The so-called **trophoneurotic diseases of the tissues** are not mentioned above, for the reason that the trophic relations of the nervous system to individual tissues are not clear, and the views of different authors as to the dependence of the tissues on the nervous system vary greatly. Many authors ascribe to the trophic action of the nervous system a far-reaching influence. For example, muscular atrophy, glandular atrophy, atrophy of the bones and joints (in tabes-and syringomyelia), different pathological conditions of the skin characterized by thinning, exfoliation of the epithelium, loss of hair, inflammation, etc., unilateral tissue-atrophies, necroses, hypertrophic proliferation of muscles, glands, skin, or bones, etc., are all referred to affections of the nerves.

It cannot be doubted that both degenerative and hypertrophic tissue-changes and inflammation often occur as sequelæ to disturbances of innervation, but these most probably are not the direct result of removal or change of nerve-influences, but are the results of increased or decreased functional activity of the tissue, or of injuries, inflammation, or disturbances of circulation, which have developed in connection with the disturbances of innervation — for example, in connection with the loss of sensibility. *Golz* and *Ewald*, after completely destroying the thoracic and lumbar portions of the spinal cord of dogs, were able to preserve uninjured the skin of the animals thus operated on; they are, therefore, opposed to the theory of trophic centres and nerves. (*Pflüger's* Arch., Bd. 63, 1896.)

III.   Autointoxications and Disturbances of Internal Secretion.

§ 23. **Autointoxication** may take place in a variety of ways. *Poisonous products of metabolism may fail of proper excretion.* Secondly, the *physiological production of poisonous substances may be transcended to such an extent as to become pathological.* Thirdly, it may happen that *poisonous products of metabolism,* which normally are decomposed and rendered harmless, may *escape destruction.* Finally, it may happen that, as *the result* of pathological changes in, or interference with the

functional *activity of certain organs, poisonous substances appear in the blood and are excreted in the urine.* According to their origin poisons may be classed as **enterogenous,** arising in the intestine, and **histogenous,** arising in the tissues.

If **injurious products arising from the decomposition of albumin** *are retained or are formed in excessive amounts in the intestinal canal,* they may give rise not only to local changes, but to symptoms of general intoxication. For example, through the action of bacteria present in the intestines, *sulphuretted hydrogen* may be formed in such amount as to pass into the blood and impart its characteristic odor to the breath, and also to be found in the urine. Further, toxic substances which arise from the decomposition of albumin through the action of intestinal bacteria, when taken into the blood are able to produce symptoms of poisoning—vomiting, headache, vertigo, stupor, acceleration and weakening of the heart's action, etc. This is especially true of those cases in which there is fæcal retention.

If the *function of the* **kidneys** *is disturbed to such a degree that substances convertible into urea are excreted in sufficient quantity,* symptoms of intoxication manifest themselves. These are characterized by coma interrupted by convulsions and by disturbances of respiration— the symptoms collectively being designated **uræmia.** According to von Limbeck, the retained substances have a narcotic action, the first effects of which are dulling of sensibility and insomnia. It has not been determined whether the toxic effects are due to a single element or to a mixture of substances.

Disturbed function of the intestines may render it difficult for the organism to rid itself of poisons, and in this way leads to autointoxication, **copræmia.** Likewise, excessive *accumulation of carbonic acid* in the blood, through interference with the exchange of gases in the lungs, may cause symptoms of poisoning.

When the *excretion of* **bile** *is hindered or arrested,* through alterations in the bile-passages or in the liver itself, the elements of the bile are taken into the blood, and the condition known as **cholæmia** is produced. Biliary salts and bile-pigment enter the blood, and give rise to lassitude, depression, inclination to sleep, slowing of the pulse, itching of the skin, a tendency to hemorrhage on slight provocation, and abnormal sensations of hearing and taste. The effects on the heart, muscles, and central nervous system are ascribed to the bile-salts. These also possess a lytic action on the red blood-cells. According to Bickel, ammonia-salts, leucin, and phenol must also be taken into consideration in the explanation of the symptoms.

If the **liver** has undergone marked pathological changes, not only does the production of bile and the synthesis of urea suffer, but substances brought to the liver from the intestines and normally decomposed by this organ may pass through unchanged. Many believe that the severe symptoms (delirium, lethargy, coma), which occur in degenerations of the liver (icterus gravis) are to be referred in part to the presence of such substances in the blood, and base their belief on the fact that under such conditions abnormal products of metabolism (ammonium carbonate) appear in the urine. In degenerations of the **pancreas,** large amounts of dextrose, acetone, and aceto-acetic acid (see § 25) may appear in the blood and urine. The two last-named substances have a

toxic action, and many are disposed to ascribe such symptoms to disturbance of pancreatic function. Finally, after degeneration of the **thyroid** or **adrenals** (§§ 25 and 26), pathological symptoms arise which may be explained in part by the assumption that poisonous products of metabolism are no longer destroyed.

In the constitutional disease known as **gout,** deposits of urates are associated with tissue-degeneration and inflammation.

The condition of **eclampsia** is an autointoxication resulting from pregnancy, and is possibly due to poisons originating in the placenta.

The term **autointoxication** is not used in the same sense by all writers. Many give to it a broader meaning than the one above, and even apply the term to certain intoxications caused by pathogenic bacteria. Such widening of the term appears to me inexpedient, in that the cause of the decomposition lies not in the body itself, but comes from without, so that intoxication is the result of a preceding infection. It seems to me to be more correct to apply the term autointoxication only to those forms of poisoning which are caused by products of metabolism, either under the influence of the body-cells or through the activity of bacteria constantly present in the intestine. As authorization for including the poisoning by products arising from intestinal decomposition among the autointoxications, I draw on the fact that the micro-organisms which cause this decomposition are constant inhabitants of the intestine, and, according to the investigations of *Schottelius,* are indispensable factors in the processes of nutrition of man and the higher vertebrates. The *enterogenous autointoxications,* which are caused by these intestinal bacteria and which occur especially in childhood through retention of the intestinal contents (ileus) or in acute digestive disturbances are in their severe forms characterized by disturbance of heart-action, small and frequent pulse, cyanosis, coldness of the extremities, and lowering of the body temperature. They may owe their origin in part to retention of intestinal contents, and in part to changes in the products of decomposition (formation of toxins) depending either on the character of the material taken into the intestines (deficiency of carbohydrates, particularly of sugar, favors the extension into the small intestine of processes of decomposition normally confined to the colon), or on a change in the virulence of the bacteria, or on deficient production of enzymes. It is not always possible in such cases to decide whether bacteria, foreign to the intestine, are not also concerned in the production of poisons. The appearance of cystin in the urine is to be regarded, according to the researches of *Baumann* and *von Udranski,* as evidence of intestinal decomposition resulting in the production of diamins.

The hypothesis that **puerperal eclampsia** is an autointoxication is supported by the majority of writers. Clinically the formation of toxic substances during pregnancy may be recognized by the occurrence of nausea, vomiting, emotional depression, hæmoglobinuria, albuminuria, and finally by convulsions and coma. The anatomical findings in women who have died of eclampsia are multiple thromboses in the smaller vessels and capillaries, and focal degenerations, usually associated with hæmorrhages in the liver (hemorrhagic hepatitis). In the lungs there may also be found syncytial cells. The fibrin-content of the blood is markedly raised. Should the child die (as takes place in about forty per cent. of cases) corresponding changes may be found in its liver and blood.

It was at first thought that the origin of the poison was in the maternal organism, and the cause was sought in alterations of proteid metabolism in which the disturbances of function were located in the kidneys, or in the liver or the thyroid. Recently the view has been advanced that the intoxication is to be referred to products of the placenta (cytotoxins). *Veit* assumes a direct intoxication through placental elements which takes place when the placental toxin can no longer be rendered inactive through the formation of antitoxin (syncytiolysin). On the other hand, *Arcoli* believes that the mother produces an excess of syncytiolysin and thereby poisons herself. *Weichart* thinks that there are formed through syncytiolysis, that is, the solution of the transported placental elements, albumin bodies (syncytiotoxins) which are poisonous to the mother. At the present time it cannot be decided which one of these hypotheses corresponds most fully to the actual conditions.

§ 24. If a gland produces an **internal secretion**—that is, if it gives to the lymph or blood substances which are necessary for the performance of the functions of other organs or of the body as a whole—**alteration** or withdrawal of this secretion is succeeded by more or less grave disturbances. Such an internal secretion is ascribed to the pancreas, thyroid, adrenals, pituitary, thymus, and the sexual glands. We are able to infer the influence exerted by these glands on metabolism and life from the disturbances which arise when the glands in question become diseased. Among the more important diseases belonging in this category are *diabetes mellitus, exophthalmic goitre, the dystrophies of pituitary origin, eunuchoidism, myxœdema, cretinism, Addison's disease,* and *the functional and anatomical changes occurring in the body after castration.*

Diabetes mellitus is a disease which is characterized by large amounts of grape-sugar in the urine (glycosuria), accompanied by great increase in the amount of urine secreted (polyuria), and often by acetone and the excretion of aceto-acetic acid and β-oxybutyric acid. At the same time grape-sugar and these acids are found in the blood and lead to diminution of its alkalinity. When the acid-content of the blood is high, headache, delirium, fainting, and finally loss of consciousness (coma diabeticum) develop.

Glycosuria may be caused by too great ingestion of sugar, so that part passes into the urine unchanged (alimentary glycosuria). Glycosuria may also follow injury to certain portions of the medulla oblongata (puncture of Bernard), or as the result of fracture of the skull with hemorrhage, epilepsy, severe psychical disturbances, tumors, parasites, or of certain forms of poisoning (carbon monoxide, curare, morphine, strychnine, amyl nitrite, nitrobenzol), in which the liver probably gives its glycogen to the blood more rapidly than normal, so that hyperglycæmia is produced.

Finally, glycosuria may be due to inability on the part of the kidneys to hold back the small amounts of glucose normally found in the blood, a phenomenon which may be produced experimentally by the administration of phloridzin (von Mering) or of caffeine sulphate (Jacobj).

These alimentary, nervous, and toxic glycosurias are to be sharply distinguished from true diabetes. In the latter the cause of the glycosuria is to be sought, not in an increased conveyance of sugar into the blood, or in a pathological excretion of the sugar normally contained in the blood, but rather in the fact that the diabetic patient is unable to decompose carbohydrates, notably dextrose, although the sugars which turn polarized light to the left (levulose and inulin) can be oxidized either wholly or at least in greater amounts than dextrose. In most cases the power to form fats from carbohydrates is also lessened, yet there are instances in which this function is unimpaired and the sugars are stored in the body in the form of fat (diabetogenous obesity).

Accordng to the investigations of von Mering and Minkowski, which have been confirmed by others, this loss of power to oxidize the sugars brought to or formed in the body, or to store them as glycogen or fat, is to be ascribed to **insufficiency of pancreatic function.** This conclusion is drawn chiefly from the fact that after total extirpation of the pancreas in dogs, diabetes of severe character, usually fatal within a few weeks, is produced, this being characterized, as is diabetes in the human subject, by polyuria, polydipsia, hyperglycæmia, glycosuria, diminution

of the glycogen of the tissues, at times by marked destruction of albumin, emaciation, excretion of large amounts of acetone, aceto-acetic acid, β-oxybutyric acid, and ammonia, as well as by the occurrence of diabetic coma. In support of the view that there is a definite relation between disturbances of pancreatic function and diabetes, it has been found that in this disease in man the pancreas has exhibited demonstrable changes, of the nature of atrophy or degeneration. Thus it has been shown by Opie, and abundantly confirmed by others, that a large percentage of all subjects dead of diabetes mellitus exhibit sclerotic or hyaline changes in the islands of Langerhans. In those instances where anatomical changes in the pancreas are not found we are forced to content ourselves with the hypothesis that our methods of investigation are defective or that there is a variety of extra-pancreatic diabetes.

An exact explanation of the relations between pancreatic disease and diabetes cannot be given, yet from the foregoing researches the hypothesis has been deduced that the pancreas produces an internal secretion which either gives the body the power to destroy glucose or increases this glycolytic capacity. Likewise, no explanation can be given for the increased destruction of the albumins and the accompanying abundant production of β-oxybutyric acid, aceto-acetic acid, and acetone. Since these substances are not always found in experimental pancreatic diabetes, their formation probably does not stand in direct relation to the excretion of sugar, but is to be regarded as a complication of diabetes (Minkowski). Their occurrence in human diabetes, moreover, is not constant, and they are found in other diseases (intoxications, carcinoma, disturbances of digestion, pregnancy, starvation, ether narcosis, etc.).

The occurrence of *diabetes* after total extirpation of the pancreas is evidence that this organ possesses a special function which is of the greatest importance in the normal consumption of sugar in the organism. *Lépine* is of the opinion that there is in the blood a glycolytic ferment, which is formed by the pancreas and passed from this organ into the blood; and that the cause of the mellituria in diabetic patients and in dogs from which the pancreas has been removed is to be sought in decrease in the amount of this ferment. According to *Cohnheim, Rahel Hirsch, Arnheim, Blumenthal,* and others the pancreas has the power, in a way not explained, of exciting to action the glycolytic ferments found in the different organs. The addition of pancreatic emulsion (*Cohnheim*) to the expressed juice of muscle increases its glycolytic capacity. At the present time it is impossible to offer a satisfactory explanation of the pathogenesis of pancreatic diabetes. According to *Stoklasa* the anaërobic respiration of the animal organs is an alcoholic fermentation caused by enzymes which may be separated from the cells and obtained in the form of powder. They will produce an alcoholic fermentation as long as they are not subjected to the action of lactic acid and thereby inhibited. In diabetes such an inhibition of the splitting of glucose into alcohol and carbonic acid occurs through the formation of lactic acid.

If only a portion of the pancreas of a dog be removed, no diabetes occurs, or at least the excretion of sugar is much less than after total extirpation (*Minkowski*). If in dogs from which the pancreas has been totally removed a portion of pancreas is transplanted subcutaneously, diabetes does not follow (*Minkowski, Hédon*), but occurs if the transplanted piece be excised.

According to *Minkowski,* there is no direct communication between the secretory function of the pancreas and that function of the organ concerned in the metabolism of sugar.

Poisoning with phloridzin produces, according to *von Mering* and *Minkowski,* a marked glycosuria in most animals and in man, and the same symptoms as those seen in diabetes, may be produced by continuous administration of the poison. Since in this case the cause of the pathological excretion of sugar lies in the kidneys and represents a flushing-out of sugar from the organism, phloridzin diabetes cannot be identified with the ordinary form of diabetes found in man — that is, with

pancreatic diabetes. In dogs in which diabetes has been produced by the extirpation of the pancreas, phloridzin produces an increase in the amount of sugar excreted (*Minkowski*).

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§ 25. **Cachexia thyreopriva** is a disease caused by *deficient or arrested function of the thyroid,* resulting either from defective development or from pathological changes in the gland. Kocher was the first to observe that it followed extirpation of the thyroid, and his results have been substantiated by many others. Numerous clinical observations and experimental researches have confirmed the fact that the presence of thyroid tissue is essential to the integrity of the organism, especially during its period of growth. The gland produces a substance known as thyroiodine which is the active ingredient of the colloid and which probably neutralizes or destroys certain poisons and at the same time exerts a complementary action on intracellular metabolism.

According to older experimental observations, total extirpation of the thyroid gland produces in man and in animals severe symptoms characterized by muscular twitchings, convulsions, and paralysis, so-called **tetany.** It is now known, however, that the production of tetany is due, not to removal of the thyroid itself, but of the parathyroid glands (parathyreoprival tetany).

If loss of the thyroid gland is at first well borne, there arise in man in the course of months or years peculiar disturbances of nutrition, beginning with weakness and heaviness of the limbs, feeling of coldness, pain and transient swelling, loss of mental activity, leading to **cachexia** associated with anæmia, by pale swellings of the skin, especially of the face, and diminution of mental powers, together with loss of muscular strength, these symptoms terminating in death. Removal of the thyroid gland in childhood causes disturbances of growth, the increase in length of the bones falling below the normal or ceasing altogether. Animals (rabbits and goats) that have had their thyroid glands removed soon after birth do not reach full growth and acquire an expression of stupidity.

Disturbances of thyroid function, as well as total extirpation, lead

to pathological conditions of the body.   Both clinical observations and experimental investigations show that the disease known as **myxœdema** (Ord) is due to changes in the thyroid.   Myxœdema is a condition in which the external appearance of the patient is indicative of thyreoprival cachexia, in that the same characteristic pale and **elastic** swellings of the skin of the face, are associated with similar changes in the skin of other parts of the body.   Further, there is loss of intellectual power, which finds expression in increasing difficulty in thinking and acting, dullness of the tactile sense, retardation of muscular action, and a monotonous nasal voice.   Finally, general weakness and pronounced symptoms of mental derangement occur, and death follows after gradually increasing cachexia associated with anæmia and coma.

Cretinism is dependent on disturbances of thyroid function.   In cretins there is always present some degenerative condition of the thyroid, the organ being either enlarged (goitre) and changed in structure (endemic cretinism), or imperfectly developed or absent (sporadic cretinism).   The general appearance of cretins is similar to that of those individuals who as a result of thyroidectomy in early childhood have become stunted in development.   The longitudinal growth of the long bones is below the normal, while the soft parts are well developed.   Individual parts of the body are unequally developed; the head is relatively large, the abdomen and neck are thick, the bridge of the nose is depressed, while the nose itself is broad and stumpy; the skin is pale, flabby, wrinkled, or puffed, as if œdematous, particularly over the face, and the belly is protuberant.   The mental faculties are feeble, sometimes markedly so.   The power of speech and of understanding may be absent, and only in the less-marked cases of cretinism are the subjects capable of work of any kind.   The cause of endemic cretinism is unknown.

The importance of the thyroid gland in nutrition and development has been placed beyond doubt by clinical observations and experimental investigations.   As to the mode of action of the thyroid, there are, however, different opinions.   If an animal, after thyroidectomy, is fed with the thyroid of some other animal — for instance, that of the sheep — the injurious effects usually observed after removal of the thyroid do not appear and occur only when the feeding is stopped.   In man the administration of fresh thyroid tissue or of thyroid extracts exerts a healing influence on the thyreoprival cachexia and myxœdema; and reports have been published of favorable results in the treatment in children suffering from cretin-like disturbances.

According to the investigations of *Baumann,* the thyroid contains an iodine substance, **thyroiodine** or **iodothyrin,** which is present in greatest quantity in old individuals, and in the smallest quantity in young children.   The normal thyroid is able to store the extremely small amounts of iodine brought to the body in vegetable foods or in drinking-water, and to convert it into thyroiodine.   The internal administration of preparations of iodine leads to accumulation of iodine in the thyroid.

According to *Baumann,* iodothyrin is the active element of the gland.   Its employment in the treatment of goitres, myxœdema, and strumiprival cachexia, etc., has the same effect as feeding with fresh thyroid tissue.   It would appear that the organism requires iodine for its maintenance, and that the thyroid supplies it with the necessary combination.   In regions where goitres are not commonly found (North Germany), the thyroid glands are, on the average, smaller (from 30–40 gm.) and contain more iodine (on the average about $3\frac{1}{4}$ mgm. instead of 2 mgm.) than in regions where goitres are numerous (Switzerland, South Germany).   Whether lack of iodine in the food and drinking-water is the cause of the hypertrophied condition of the thyroid in goitre, or whether some injurious agent, perhaps some lower organism, interferes with the specific function of the gland, cannot be said.   Among domestic animals having a large amount of iodine in the thyroid are the sheep, cow, and calf, while in hogs the iodine-content is small.

Anatomical investigations have failed to throw definite light on the question of the internal secretion of the thyroid. It has been proved that the colloid produced by the thyroid cells passes into the lymph-vessels. It is probable that iodothyrin is obtained in this colloid substance. During intra-uterine life the thyroid appears to be destitute of that function, which in later life is so important.

Graves' disease, or exophthalmic goitre, which is characterized by goitre, exophthalmos, rapid heart, tremor and great excitability on the part of the patient, is dependent on disease of the thyroid characterized by *hypersecretion* (*hyperthyreosis*). According to *Beebe* the experimental feeding of thyroid glands produces symptoms and metabolic changes similar to those of Graves' disease. Removal of a considerable portion of the gland will in many cases effect a cure; and recurrence of the disease after operation is in most cases accompanied by recurrence of the tumor. *Oswald* has shown that the colloid of the glands from cases of exophthalmic goitre is, in the majority of cases, deficient in iodine. He believes that the symptoms are due to flooding of the body by altered secretion. *Ewing*

FIG. 4.—(Bellevue Hospital,) Acromegaly, showing the enlargement and spade-like character of the hands.

has studied the histological changes in the glands of forty cases of exophthalmic goitre, and believes, in common with other writers, that the findings are to a certain extent specific. In many instances of exophthalmic goitre, however, the histological changes in the thyroid present no essential differences from those of ordinary forms of goitre. *Symmers* has shown that the so-called idiopathic cardiopathy is associated with sclerotic and hyperplastic changes in the thyroid gland, and suggests that this variety of cardiac enlargement is part of an ill-developed variety of Graves' disease (thyro-toxic cardiopathy). Some writers regard the thymus as associated in some way with the pathogenesis of exophthalmic goitre, but no definite proof of this is at hand. Preliminary removal of thymic tissue has been practiced with beneficial results in the operative treatment of Graves' disease (*Halstead*).

Acromegaly may be defined as a dystrophy characterized by increase in size of the bones of the face and extremities, associated with perverted secretion of the pituitary body. Hyperactivity of the anterior lobe of the pituitary coming on before completion of epiphysial ossification results in *giantism;* that is to say, the individual is overgrown, but well proportioned. If epiphysial ossification is complete, however, hyperactivity of the pituitary results in *acromegaly* with or without giantism. That the relationship between acromegaly and giantism is close, is shown by the fact that a considerable percentage of acromegalics are giants and that a still larger percentage of giants eventually develop acromegaly. Clinically,

acromegaly is characterized by increase in the size of the bones of the head; particularly those of the face. Thus, hypertrophy of the cranial bosses, the supraorbital ridges, the malar bones, both maxillae, and the nasal bones gives rise to profound changes in facial expression. In addition, enlargement of the bones of the hands produces a spade-like appearance. The nails are usually broad, but there is no curving and the terminal phalanges are not bulbous. The feet are uniformly enlarged. Later the spine may be affected. In acromegalic giantism, in addition to changes in the osseous system, there is enormous increase in the size of the viscera, notably the heart, lungs, liver and spleen (the so-called *splanchnomegaly*) and atrophy of the genitals. Acromegaly and acromegalic giantism both depend on disease of the pituitary, such as adenomata and other tumors, or replacement by syphilitic or tuberculous granulomata, cysts, etc. Both commonly are attended by changes in other of the ductless glands. For example, the association of *status lymphaticus* is common, and changes in the thyroid occur so frequently in conjunction with enlargement of the pituitary, that certain observers have been led to the conclusion that interference with the interaction of these glands is a formidable factor in the production of the disease in question. Moreover glycosuria is of frequent occurrence in acromegaly and acromegalic giantism. Sometimes it is a symptom of genuine diabetes and is associated with *sclerotic* or *hyaline changes in the islands of Langerhans*. At other times it is an expression of diminished tolerance for carbohydrates, brought about by increased activity of the pituitary. In still other instances, subjects of acromegaly develop signs of pituitary insufficiency, marked by greatly increased tolerance of carbohydrates, adiposity, impotence, etc. Acromegaly usually begins in the third or fourth decade and is rather more frequent among men than women. Heredity appears to play an important role. For example, the disease has been observed in both parents and a child, in father and son, in father and daughter, in mother and daughter, and in a case of acromegalic giantism that I investigated postmortem at the Willard Parker Hospital in New York, the disease occurred in two brothers.

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§ 26. **Addison's Disease** is to be regarded as the result of *functional disturbance of the suprarenals.* It is characterized by the appearance of a light-yellow-brown to dark-brown, diffuse, and spotted pigmentation (*melasma suprarenale*), which shows itself first in the portions of the skin normally exposed, later in other parts, notably in those cutaneous surfaces which are subject to irritation, such as the neck, waist, wrists and ankles; and in the more exposed mucous membranes, such as those of the mouth and lips, occasionally the penis or vagina. Even at the beginning of the disease, or before the pigmentation of the skin, there occur loss of appetite, nausea, diarrhœa or constipation, and vomiting — all symptoms of disturbed intestinal and gastric function; later, muscular weakness: asthenia, fatigue on slight exertion; headache, vertigo, fainting, epileptiform attacks, and coma. Occasionally recognizable increase of the pigment of the skin does not occur and the disease is characterized only by gastro-intestinal symptoms, progressive weakness, and anæmia.

In about eighty-eight per cent of all cases of Addison's disease the suprarenals are found to be diseased, the majority being changed into caseous or fibro-caseous masses of tuberculous nature. More rarely there are found tumors in the adrenals or simple atrophy, agenesia, or hypoplasia. Alterations in the suprarenals bear a causal relation to the symptoms described above; the disease may, therefore, be designated as **suprarenal cachexia.** It is not improbable that the suprarenal bodies, like the thyroid, produce a substance which is necessary for the preservation of the organism; that poisonous substances are destroyed by them is known, since epinephrin, which is the active principle of the adrenal mudulla, has been shown to neutralize diphtheria toxin (Marie, Stutzer).

The *suprarenal capsule* represents, developmentally, two sets of organs which, in higher forms, are fused, the cortex originating in the mesoderm and the medulla in the neuroectoderm. The cortex, which is of companion origin with the testicle in the male and the ovary in the female, is in some way connected with sexual activities. For example, there is a tumor of the adrenal cortex which, when it develops before the onset of puberty, brings about certain changes in bodily growth and in the development of the genitals and secondary characteristics that can be attributed only to interference with the normal function of the cortical cells. The medulla, on the contrary, is composed largely of nervous elements and of polymorphous cells which, when treated with chrome salts, take on a brownish appearance and are known as chromaffine cells. Identical cells are encountered in situations beyond the suprarenal capsule, mainly in the tissues along the course of the abdominal aorta — the so-called Zuckerhandl's paraganglia. It is held by many that the specific function of the suprarenal and other chromaffine cells is to furnish an internal secretion which maintains the vascular and muscle tone and controls the amount and distribution of certain pigment in the skin and mucous membranes. Interference with the function of the chromaffine system, particularly with those

elements which reside in the suprarenal medulla, is followed by changes of profound importance, notably by the disease described by Addison. In other cases, however, it is possible for extensive changes to arise in both suprarenal capsules without Addison's disease. In these circumstances it is held that islands of functionating suprarenal tissue are still intact and, in addition, that the extra-capsular chromaffine cells are called on to compensate for those lost by destruction of the suprarenals. Conversely, Addison's disease may arise without detectable changes in the suprarenal capsules, in which case it is argued that the extra-capsular chromaffine system is the seat of disturbance, the supply of chromaffine cells in the suprarenal bodies being inadequate to balance the loss.

Of over 5,600 autopsies at Bellevue Hospital destructive lesions of the suprarenal capsules were encountered 48 times. In 23 cases the lesion was unilateral, in 25 bilateral. Of the 48 cases both suprarenal capsules were completely or almost completely destroyed in 18 cases of long standing, but in not one of the number were signs of Addison's disease detected. In two other cases, however, both suprarenals were completely replaced — once by tumor metastases and once by caseating tuberculosis, and in both instances the patients during life presented diffuse, dirty yellowish pigmentation of the skin, low blood pressure and asthenia. Similar cases of "suprarenal insufficiency" attended by symptoms comparable to those of Addison's disease have been recorded by Osborne. It appears from such observations that typical and fully developed Addison's disease depends on more complete changes than destruction of the adrenals alone. It is probable that involvment of the coeliac ganglia plays an important part in completing the pathological picture.

The view is widely prevalent that the *epinephrin* of the suprarenal capsule is indispensable to life, that it is an important factor in the maintenance of muscle and vascular tone, and that in certain circumstances it acts as a detoxicating agent, notably in diphtheria (Marie, Ann. de l'Instit. Pasteur, 1918). Recently Cannon and his coworkers (Am. Journ. Physiol., 1919) have advanced the view that the suprarenal medulla is stimulated to secrete epinephrin by emotional excitement, pain and asphyxia — conditions which are known to be accompanied by activity on the part of the sympathetic nervous system — in other words, that the physiological reaction to fear and related emotional states depends on hypersecretion of epinephrin into the circulation. This view has been combated by Stewart and Rogoff, who insist that there is no increase of suprarenal secretion in the emotional states mentioned. The same investigators have demonstrated (Am. Journ. of Physiol., 1919) that it is possible for animals to live indefinitely in good health after one suprarenal capsule has been excised and the nerve of the other sectioned, an operation which either abolishes the output of epinephrin or reduces it to a minimum, in other words, that epinephrin is not essential to muscle and vascular tone.

§ 27. As a pathological condition due to loss of a specific glandular function should be classed those changes in the body resulting from **castration** — that is, the removal of the sexual glands. If the ovaries are removed after puberty, menstruation ceases at once, rarely after some time. Sexual desire and the erethism accompanying the sexual act are usually diminished in intensity, but may be unchanged. The remaining portions of the genital apparatus undergo atrophy; this is marked in the case of the uterus. Certain nervous manifestations may follow, the most common of which are excitement, with flushing of the skin, especially of the face, associated with attacks of sweating; these symptoms are of most frequent occurrence in the period immediately following the castration. The disposition remains unchanged or even becomes more cheerful, especially in those cases in which the woman by castration is relieved of pain. At times depression or melancholia may follow. If the ovaries are removed or destroyed during childhood, the secondary sexual characters are not clearly defined; the muscles are more strongly developed, the configuration of the pelvis is changed, and the breasts do not increase in size.

Castration in an adult male produces no marked change in build. On the other hand, if boys are castrated, the body loses in masculine

character.   There is increased deposit of fat, particularly the abdomen, while the musculature is feebly developed.   The external genitals remain small, the prostate is diminished in size, and there is little or no growth of beard or pubic hair.   The larynx is infantile, the voice child-like. The mental powers are lacking in energy and strength.

A type of physical degeneracy is described under the title of **eunuchoidism or dystrophia adiposo-genitalis.** The male eunuchoid is an individual whose bodily configuration is characterized by abnormal length of the extremities and in whom the distance from the umbilicus to the soles of the feet is noticeably greater than that from the umbilicus to the crown of the head.   There are marked accumulations of fat in the region of the breasts and mons veneris while the abdomen is protuberant and the waistline narrow.   The penis, testicles and scrotum are extraordinarily small, the pubic hair scanty and of the feminine type, the voice is high and shrill, the skin pale and satiny.   Most of these individuals are sterile.   In female eunuchoids the breasts are poorly developed or fatty and contain few glandular elements.   A male subject of eunuchoidism, age 22 years, was investigated postmortem at Bellevue Hospital.   In addition to the peculiarities of configuration, it was found that the seminal vesicles contained only a thin, milky fluid. Both testicles were extremely small, measuring $1 \times 1\frac{1}{2}$ cm.   They were dark brown in color and firm.   The prostate, on the contrary, was apparently normal in size and consistence.

According to *White, Kirby, Kummel, Bruns,* and others, castration in fully developed animals causes decrease in the size of the prostate; and castration of old men suffering from prostatic enlargement was at one time practiced as a surgical procedure; even now castration is a religious rite among certain fanatics, notably among Russian peasants.

In what way *extirpation of the sexual glands affects the body* has not been determined.   By many it has been assumed that, as a result of castration, the trophic influence exerted on the tissues by the sexual glands is withdrawn; but it is more likely that *chemical substances,* which exert a certain influence on functions, growth, and development, are formed in the sexual glands.

According to the investigations of *Loewy* and *Richter,* after castration of female dogs there occurs lowering of the oxidation-power of the cells and decrease in the amount of oxygen used by about twenty per cent.   According to *Breuer* and *von Seiller,* the total mass of hæmoglobin and red blood-cells is diminished.   The administration of dried ovarian substance or of oöphorin from the ovaries of the cow or hog to the animal operated on causes an increase in the amount of oxygen consumed even greater than the average observed before castration.   Preparations of testicles showed no such influence.   In male dogs the same conditions prevailed; spermin caused only slight increase in the gaseous interchange, oöphorin gave a marked increase (as much as forty-four per cent.).

According to the investigations of *Born* and *L. Fraenkel* the *corpus luteum* appears to possess an internal secretion.   On the one hand, it is thought to govern the metabolism of the uterus and to make possible the insertion of the impregnated ovum, and, on the other hand, to excite menstruation.

The thymus has often been credited with an internal secretion.   Most investigators are now convinced that this is not true and that the thymus is not essential to life.   In animals extirpation produces no noteworthy detectable alterations, although it cannot be denied that it may have some influence in delaying closure of the epiphyses, thus retarding development.

Chief interest in the thymus centers in its association with sudden death in the condition known as **status lymphaticus.**   *Status lymphaticus is not a disease.* On the contrary, it is to be defined as a combination of hereditary constitutional anomalies, entering into which are certain peculiarities of configuration (*Norris*), with preservation or hyperplasia of the thymus gland at an age when involution is to be expected, hyperplasia of the lymphoid cells in the spleen and intestine, and, to a less extent, in the lymph nodes, hypoplasia of the cardio-vascular system, developmental deficiencies in the genitalia and incidental visceral anomalies of uncertain occurrence and irregular distribution.   The condition sometimes is terminated by sudden death, usually in children, but occasionally in young adults. Although status lymphaticus is compatible with life, it is, nevertheless, a menace, and for at least three reasons: (1) Because it is attended by certain necrotic changes in the lymphoid tissues, providing a mechanism which, when once set in

motion, is capable of so sensitizing the body as to produce anaphylactic phenomena varying from simple urticarial rashes to convulsive seizures or sudden death. The theory that sudden death in status lymphaticus may be due to pressure of the enlarged thymus on the trachea is not tenable.   In the Bellevue Hospital autopsies not a single incidence of death from this cause was found.   (2) The same instability of the lymphoid tissues is apparently responsible for lowering the threshold of infection, particularly those infections which gain entrance through the pharyngeal and faucial tonsils and the lymphoid structures of the intestinal tract.   (3) It is attended by defective development of the muscular coat of the arteries and renders them incapable of withstanding increased blood pressure of a degree ordinarily well borne.   Status lymphaticus is easily recognized clinically. The angelic child of the elder Gross is of this category.   In male adults there are two types of configuration — the rectangular and the Appoline.   In the first the shoulders are squared and the chest somewhat flattened antero-posteriorly.   In the second the muscular development often attains magnificent proportions.   In both varieties the skin is of unusually delicate texture; the facial, axillary and pubic hairs are scanty, the latter being more or less sharply defined in a transverse direction; the waistline is narrowed and the thighs are rotund and arching.   In the female the delicate texture of the skin, the accentuation of the graceful outlines of the body and the presence of small axillary fat pads with the scanty growth of hair on them, combine to render recognition easy.   Status lymphaticus is fairly common. It was recognized in about eight per cent. of six thousand autopsies at Bellevue Hospital.   The average weight of the thymus gland was about twenty-five grams. In status lymphaticus the aorta and the cerebral vessels are hypoplastic in about forty per cent. of cases.   Rupture of the cerebral blood vessels with fatal hæmorrhage into the pia arachnoid or into the substance of the brain not infrequently occurs, spontaneously or under the influence of such trivial causes as argument, fighting, etc.   Status lymphaticus is a distinct contraindication to the acceptance of a workman for duty in an atmosphere of compressed air, since decompression is apt to be followed by sudden death.   Status lymphaticus is common among the emotionally unstable — drug habitues, neurasthenics and the insane, suicides, degenerates and criminals.   Its association with exophthalmic goitre is exceedingly common and the same is true of chlorosis, Addison's disease, acromegaly, and the like.   Finally, it has been shown by *Daut, Elser* and *Symmers* that diphtheria, cerebro-spinal meningitis, typhoid fever and acute infective endocarditis occur with noticeable frequency in subjects of status lymphaticus *and that these and other infections in such individuals are apt to pursue a rapidly fatal course.*

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IV. Fever and Its Significance.

§ 28. When a local organic disease takes on the character of a **general disease,** or when a disease at its inception manifests such a character, there frequently is seen the *symptom-complex* known as **fever.** Particularly in infectious diseases associated with symptoms of intoxi-
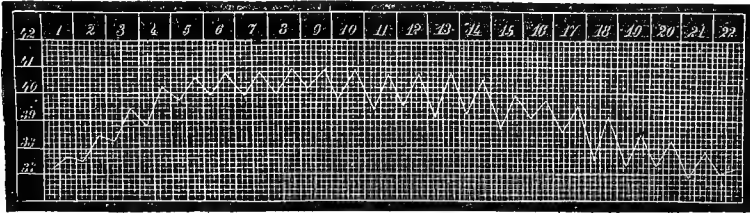
FIG. 5.—Temperature-curve of a continued remittent fever, with slowly rising and gradually falling curve (typhoid fever).

cation does the appearance of fever play an important rôle. The characteristic sign of fever is *increase of bodily temperature;* but accompanying this are other symptoms, especially *increase of the pulse-rate, disturbances in the distribution of the blood, changes in the gaseous interchange within the lungs,* and *changes in the urinary secretion.* There is usually a subjective feeling of illness, but this is not a necessary part of the symptomatology of fever, but the effect of poisoning associated with infection.

Observation has taught us that, in spite of changes of temperature externally, the body-temperature is maintained at an average height of 37.2–37.4° C. (98.96–99.32° F.). The absolute variation between morning and evening is 1–1.5° C. (1.8–2.7° F.), the maximum occurring at evening.

The elevation of temperature of the body above that of its surroundings is due to the fact that through chemical changes, particularly in the muscles and glands, heat is produced, and to such an extent that the temperature may be raised one degree Centigrade (1.8° F.) in half an hour. This phenomenon of heat-production is offset by one of heat-dispersion, occurring chiefly through the skin, lungs, and the excreta. Both heat-production and heat-dispersion are under the influence of the nervous system, and through its regulation of both processes a constant temperature is maintained.

On exposure to lower temperatures heat-production is increased (chiefly through the agency of the muscles), while heat-dispersion is lessened through contraction of the cutaneous vessels and inhibition of perspiration.

On exposure to higher temperatures heat-dispersion is increased through increased frequency of respiration, dilatation of the arteries of the skin, and increased secretion of sweat.

In that condition which we call **fever** there is *disturbance of the regulation of heat-production and heat-dispersion,* in favor of heat-production, so that the *temperature of the body is elevated above the normal* (Figs. 5–7). Elevations of temperature (rectal measurements) to 38° C. (100.4° F.) are called *hypernormal;* from 38° to 38.5° C. (100.4–101.3° F.), *light fever;* from 38.5° to 39.5° C. (101.3–103.1° F.), *moderate fever;* 39.5–40.5° C. (103.1–104.9° F.), *marked fever;* over 40.5° C. (104.9° F.) (evening temperature), *high fever;* and over 41° C. (105.8° F.), as *hyperpyrexia.*

Four **periods** may be distinguished in fever. The first, which is known as the **pyrogenetic** or **initial stage,** corresponds to that time dur-
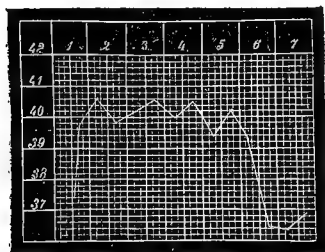
FIG. 6.—Temperature curve of a continued fever with rapidly ascending and rapidly falling curve (pneumonia).
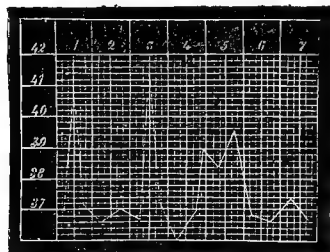
FIG. 7.—Temperature-curve of an intermittent tertian fever (malaria).

ing which the previously normal temperature reaches the average height characteristic of the disease. This period is sometimes short (Fig. 6), half an hour to two hours long and is usually accompanied by a *chill;* sometimes longer (Fig. 5), one to several days, and usually runs its course without a chill, though chilly sensations may repeatedly occur.

In the second period, known as the **fastigium,** whose duration varies according to the disease from a few hours to several weeks, the temperature reaches one or several *high points,* between which there are more or less marked remissions.

In the stage of **decline** or **defervescence,** the body-temperature returns to the normal. If this takes place through a rapid fall (Fig. 6), it is called **crisis;** if slowly it is termed **lysis** (Fig. 5). The former is usually accompanied by profuse sweating, and in a few hours, or at most in one to one and a half days, the temperature falls two or three degrees, occasionally as much as five or six degrees Centigrade. In lysis the temperature falls gradually for three to four or more days; the decline may be either continuous or intermittent.

The boundary line between fastigium and defervescence is not always sharply defined, and before the latter sets in there may occur elevations of temperature. Between fastigium and defervescence there may be several days of uncertainty with striking fluctuations upward or downward. Occasionally there is a short period in which the temperature is somewhat lowered, but yet remains high above the normal, to sink after a few days to the normal, either rapidly or by gradual decline.

In the stage of **convalescence** the temperature returns to the normal. The heat-regulation during this time is still imperfect, so that often slight elevations and not infrequently subnormal temperatures occur.

If during the course of a fever the daily variation is slight, and the difference between maximum and minimum is not more than that under normal conditions, the fever is called **continuous** (*febris continua*) (Fig. 6). If the differences are greater, the fever is termed **subcontinuous** (*febris subcontinua*), **remittent** (*febris remittens*) (Fig. 5), or **intermittent** (*febris intermittens*) (Fig. 7).

In the last-named, afebrile periods (*apyrexia*) alternate with periods of fever, each *paroxysm* having an initial period, a fastigium, and a defervescence. In the infectious disease known as **febris recurrens** there is first continuous fever, which after a few days falls by crisis; after a week or so a second rise of temperature occurs, which may be followed by a second stage of apyrexia, and this by a third period of fever, and so on.

Many diseases — such as typhoid fever, pneumonia, measles, relapsing fever, etc.— are characterized by a typical temperature-curve; others — as the fevers of pleuritis, endocarditis, diphtheria, tuberculosis, phlegmon, etc.— have no typical course.

The **elevation of the body-temperature** in fever is dependent, first, on *increase in heat-production through increase of chemical changes in the tissues.* The *respiratory interchange of gases* — the excretion of carbonic acid and the taking-up of oxygen — and the *excretion of nitrogenous elements in the urine,* (urea, uric acid, creatinin) *are increased* — the latter from seventy to one hundred per cent, under certain conditions as much as threefold. There is also increased destruction of the albuminoid substances of the body, even in the latent period of the fever.

The increase of heat-production varies in different fevers, and reaches its highest point during the violent muscular contractions at the time of the initial chill.

The second cause of elevation of the body-temperature is *deficient heat-dispersion.* At the height of the fever the patient as a rule gives off more heat than the normal individual, but this dispersion is not sufficient to offset the excessive heat-production. Heat-production is constantly increased; heat-dispersion is irregular.

In the initial stage the cutaneous vessels are contracted as a result of stimulation of the vasomotor mechanism, the skin is pale, the heat-dispersion slight, under certain conditions even less than normal.

Chills occur when, through contraction of the peripheral arteries, the supply of blood, and consequently the heat-supply, to the skin, is suddenly diminished, while in the interior of the body the temperature is rising.

In the **second stage of fever** the skin is often hot and reddened, and in certain diseases sweating occurs; but the increased heat-dispersion thus produced is not sufficient to lower the temperature to the normal. The increased excitability of the vasomotors or the deficient irritability of the vaso-dilators is also present during this period, and as a result the skin-temperature, as well as the heat-dispersion, varies greatly. The skin is at times pale and cold, at other times red and hot, or the hands may be cold while the trunk is hot. The centres governing heat-dispersion are therefore acting faultily.

In the **period of defervescence** the relations of heat-dispersion and heat-production are changed in favor of the former. The cutaneous vessels become dilated, the skin gives out a great amount of heat from the abundance of blood circulating through it, and when the critical fall of temperature occurs there is usually profuse sweating.

The **cause of fever** is not known with certainty, yet this much can be said, that fever is most frequently the *result of the entrance of a harmful agent into the fluids of the body*. In many cases this harmful agent arises from a local focus — for example, from erysipelatous and phlegmonous inflammations of the skin. In man, the *infectious diseases*, which are due to specific micro-organisms multiplying in the body, are characterized, among other things, by all the phenomena of fever.

Parasites multiplying within the body cause increased tissue-destruction, and at the same time substances are probably produced which act as *poisons* to the central nervous system. The action of the latter may be assumed to be of such a nature that, on one side, the activity of the muscles and glands, and consequently the heat-producing metabolism, is increased; while, on the other hand, through the diminished and disturbed functions of the nerves governing sweating, as well as of the vasomotors, the processes of heat-dispersion fall behind those of heat-production. Though the organism makes an effort to regulate the temperature, it is no longer able to maintain it at the normal level, because of the disturbances of the regulating apparatus. What share in the increase of body-temperature is due to the direct action of bacteria and of the ferments formed by them, or what share is due to the increase of metabolism, or through disturbance of heat-dispersion, cannot at present be determined. It is, however, certain that the factors vary in different cases. That certain changes in the nervous system are sufficient to cause increase of temperature, is shown by the fact that such increase occurs in epileptic attacks, in the periods of excitation in progressive paralysis, after severe frights, after the passage of a catheter into the bladder, etc. In this connection, however, it is to be emphasized that fever is a far more complex affair than mere elevation of temperature. According to the investigations of Richet, Aronsohn, and Sachs, marked increase in body-temperature with increase of the respiratory interchanges of gases and increased excretion of nitrogen (Aronsohn and Sachs) may be produced in animals by puncture through the cerebral cortex and into the corpus striatum. The same phenomenon may be produced by electrical stimulation of the same portion of the brain. Nevertheless, fevers dependent on nervous disturbance are rare, and are overshadowed in importance by those caused by infection.

The rise of temperature in fever is usually accompanied by **increase in the frequency of the pulse**; but in some cases this effect of the elevation of temperature may be so modified by stimulation of the vagus — as, for example, in basilar meningitis — that the pulse-rate is lowered.

In diseases attended by fever, the patient may or may not be appreciative of the fact that he is ill, according to the extent to which his senses are benumbed. In anthrax, for example, clarity is frequently maintained until the moment of death. In the majority of fevers, however, there are symptoms of excitation or depression, delirium, apathy, involuntary evacuations, convulsions (in children), etc. The muscles of the body become weak and not infrequently painful. Digestion is impaired; the appetite for food is slight, but on the contrary there is great thirst; the mouth is dry. There is increased frequency of respiration; after the appearance of muscular weakness the respiratory movements are superficial. The excretion of urine is usually diminished; the amount of urea is increased, while that of sodium chloride is apt to be diminished.

In prolonged fevers there is marked wasting of the body, in that a large portion of the albuminous material and fat is destroyed.

To what extent these symptoms in individual cases are dependent on the increase of temperature or to what extent on the damage caused by the specific morbid process, it is difficult to say. The marked effects on the nervous system must in part be regarded as a result of infection and co-incident intoxication.

The direct cause of death in febrile diseases is most often to be ascribed to degenerative changes in the heart muscle resulting in dilatation of its chambers with or without congestion and œdema of the lungs. Contributing factors are to be found in degenerative lesions in such important viscera as the liver and kidneys and in the central nervous system. The effects so produced are not attributable alone to elevation of temperature, but to attendant intoxication. Indeed, it should be remarked that high temperatures may be borne for a length of time without fatal results (see § 3).

CHAPTER III.

The Protective and Healing Forces of the Human Body.
The Acquisition of Immunity.

§ 29. The body is by no means defenceless against the many harmful influences to which man in the course of his life is exposed. It possesses various **protective contrivances** by which it is able to ward off injury, or to counteract its influence, so that disease may be prevented or confined to a local lesion. The mode of action of different injurious agents varies greatly, so does the manner of defense vary. The protective forces may act at different times — sometimes before the tissues have been damaged, at other times after the injury has reached a certain stage, and threatens, through direct extension or metastasis of its provocative agent, to spread through the body.

When the surroundings become relatively cold or relatively warm, *regulating functions* are brought into play through which the organism can *increase or diminish heat-production and heat-dispersion,* and in this manner protect itself within limits against the external temperature. If these regulating functions are imperfectly performed, as in alcoholic intoxication, the individual may succumb more easily to the effects of cold than in normal circumstances.

We cannot speak of special protecting contrivances against the cruder forms of mechanical injury; yet it is to be noted that the tissues are fitted to offer resistance to the more subtle varieties of traumatism. If small, firm bodies, such as dust-particles, reach the mucous membrane of the respiratory or intestinal tracts, the *epithelium* forms a barrier against their entrance. If cilated epithelium be present, the dust-particles may be carried away by the *movements of the cilia,* or become surrounded by the *mucus* produced by the epithelium of the mucous glands, and in this way are transported out of the body.

Not infrequently cells appear on the surface of the mucous membrane that encompass the dust-particles, and, taking these into their substance, are carried away with the secretions. This phenomenon is known as *phagocytosis.* The active agents participating in it are cells which pass from the tissues to the surface, and are derived from the blood, from the lymphadenoid tissue of the mucous membrane, and from the epithelium. The phenomenon of phagocytosis depends on the fact that the cells, by movements of their protoplasm, take up particles, which, like insoluble dust, exert no harmful influence on their protoplasm. If these cells pass outside the body, the taking-up of the dust is useful in cleansing the organs of dust. If the dust-laden cells, as happens particularly in the lungs, pass into the lymph-channels and are deposited in or carried to the lymph-nodes — that is, if metastasis takes place — we can regard this act as useful only in the sense that infiltration of the pulmonary connective tissue and lymph-nodes is less harmful than the deposit of dust in the alveoli.

When dust-particles, free or enclosed in cells, reach the *lymph-nodes,* they are arrested, so that the lymph-nodes are to be regarded as *filters,* which guard the blood and organs from the entrance of dust, and, indeed, from many other foreign substances.

Against the *action of poisons* the body is able to protect itself in various ways. Against corrosive poisons the *horny layer* of the epidermis and the *mucus* of the mucous membranes offer a certain protection; for example, increase in the production of mucus in the stomach, may diminish the harmful effects of a corrosive fluid. Through transudation of fluid from the blood-vessels to the surface of the mucous membrane a caustic fluid may be so diluted as to modify its action. On the other hand, the injurious substance may thus be spread over a greater surface, and cause more widespread damage.

On many poisons, abrin, ricin, the toxins of cholera, tetanus, and diphtheria, and snake-venom, the digestive juices have such an influence that doses invariably fatal when injected under the skin are borne with impunity when taken by the mouth. According to Ransom, guinea-pigs are able to withstand, by the mouth, an amount of tetanotoxin equivalent to three hundred thousand times the minimal fatal dose. According to Nencki and others, this *neutralization is produced by the digestive enzymes.* It is probable (Nencki) that the digestive enzymes cause a slight change in the molecules of the toxin, and the products thus arising may accordingly be termed *toxoses* or *toxoids.* The intestinal enzymes have no neutralizing influence in the poisoning produced by *Bacillus botulinus* and, after the eating of infected foods fatal intoxications may occur.

Those poisons which act injuriously on the blood or nervous system, may be counter-acted by *rapid excretion* through the kidneys, intestine, salivary glands, mammary glands, sweat glands, and lungs; by *transformation into combinations soluble with difficulty,* which are then stored in different organs (liver), by *change of the poisons into combinations that are relatively harmless and easily soluble,* and which are taken into the circulation and excreted, and by *chemical change of the poison.*

Of *natural immunity or resistance to poisons* we know but little, yet there is no doubt that many substances are poisonous only for certain organisms, that man is resistant to poisons which are injurious to certain lower animals. The same holds true of toxins (§ 11), such as are formed by bacteria or by animals (snakes) and plants (ricin and abrin). If we consider that many animals are only slightly or not at all susceptible to poisons which have marked action on the human body — the hedgehog is immune or resistant to cantharidin and to the bite of poisonous snakes; birds are immune to atropine and opium; goats to lead and nicotine; while dogs, rats, or other animals used for experiment show a disproportionately greater resistance to bacterial poisons or plant-alkaloids than does man — it is probable that the reverse is true. The natural immunity of man to many of the infectious diseases of animals must depend on resistance to the toxins produced by the particular bacteria. According to Ehrlich, this resistance may be explained on the ground that the particular toxin possesses no chemical relationship to any one of the body elements. Relative immunity may therefore depend on the fact that the healthy individual possesses a certain amount of antitoxin (for example, against diptheria toxin).

§ 30. Against the **infections and intoxications caused by parasites** the body also possesses **protective contrivances** and **powers of defence;** and these play an important rôle in the diseases caused by bacteria.   In the first place, man possesses a **natural immunity** to many of the micro-organisms which are pathogenic for animals (for example, swine plague, swine erysipelas, cattle plague, symptomatic anthrax), so that the given micro-organisms are not able to reproduce within the body, either because they do not find in human tissues the necessary conditions of life, or because the presence of certain chemically active substances hinders their increase or kills them directly.   Further, immunity may rest on the fact that poisons produced by given bacteria in a given organism are ineffective because no chemical affinity exists between the poisons and any of the body elements.   **For the protection of the body against the pathogenic micro-organisms there are available certain forces,** which, according to their action, may be divided into four groups: the first hindering the entrance of bacteria into the tissues; the second opposing local dissemination of those bacteria which have gained entrance and have begun to multiply; the third preventing the entrance of bacteria into the blood; the fourth tending to neutralize the effects of intoxication.

For the **prevention of the entrance of pathogenic bacteria into the tissues** the same properties of tissues are effective as those hindering the entrance of dust; and in such capacity *epithelium* and *mucus* play an important rôle.   In the respiratory tract the *movements of ciliated epithelium* furnish protection, and in the stomach the *destructive action of the gastric juice* on pathogenic bacteria is an efficient means of defence, notably against the cholera vibrio.

It appears that mucus not only can envelop bacteria, hinder their entrance into the tissue, and favor their removal, but that — what is of greater importance — the mucus acts on the bacteria, causing them to degenerate, either because it contains substances which are injurious or because it offers an unfavorable medium for growth.

In the intestine *bacteria* normally present (B. coli communis, B. lactis aërogenes) afford protection against multiplication of pathogenic bacteria that may have entered; for example, against cholera-spirilla, while, on the other hand, the development of staphylococci and streptococci does not appear to be hindered.

Not every pathogenic micro-organism, therefore, which gains a foothold on the skin or mucous membranes or effects entrance into the intestines or lungs produces infection.   It has been shown that in normal individuals there frequently occur in the upper respiratory passages and mouth not only harmless bacteria, but also those which produce disease, as, for example, pneumococci and the bacillus of influenza.   It must, therefore, be granted that bacteria which are found on mucous membranes and perhaps multiply there often are carried off or destroyed without having produced infection.   This occurs not only to the bacteria just mentioned, but to many others, including tubercle bacilli, as well as to cholera spirilla that have been brought into contact with the acid secretions of the stomach.   Of the pathogenic bacteria entering the alveoli of the lung in the inspired air, many do not reproduce, but die.

When **bacteria succeed in gaining entrance and have begun to multiply** — no matter whether they have passed through the epithelium without the aid of others (typhoid-bacilli, cholera-spirilla), or have

passed into the tissues through wounds (tetanus-bacilli, pus-cocci, tubercle-bacilli) — if they produce destruction of tissue or poison the fluids of the body, there may be brought into action **counter-influences** *which hinder their development or weaken or destroy the poisons produced by them.*

Many writers ascribe the **prevention of the spread of infection** and the **destruction of bacteria,** in local foci of growth, to the activity of cells which collect at the seat of infection and take up the bacteria into their protoplasm — that is, to **phagocytosis.** According to Metschnikoff and others the amœboid cells of the body carry on a fight against invaders and endeavor to overcome and destroy them. Such characterization of the phenomena of phagocytosis is not supported by facts, but is to be regarded as a poetical expression by which consciousness and will-power are attributed to amœboid cells (leucocytes and proliferating tissue-cells). It is self-evident that such attributes do not exist in cells. Scientifically considered, the gathering of the cells at the infected focus and the resulting phagocytosis represent simply an expression of certain processes which are natural to amœboid cells, and which are dependent on the fact that such cells under the influence of mechanical, chemical, and thermal influences perform certain movements. We know that the motile cells of the body are in part attracted, in part repelled or paralyzed by chemical substances in certain concentrations (see the Chapter on Inflammation) ; and, further, that contact with hard bodies can stimulate them to send out protoplasmic processes.

Such phenomena are designated **negative** and **positive chemotropismus** or **chemotaxis** and **tactile irritability.** We must assume that bacteria multiplying in the tissues act on the amœboid cells through the chemical substances which they produce, sometimes repelling or paralyzing, sometimes attracting, in the latter case affording conditions favorable for phagocytosis. The bacterial proteins arising from the bodies of dead or dying bacteria and passing into solution in the body juices have, in particular, a positive chemotactic action on the phagocytes.

The *result of the taking-up of bacteria into cells* depends partly on the properties of the devouring cells, partly on the properties of the microparasites, and can result as well in the death and dissolution of the parasite, as in the death of the cells; or in symbiosis of the cells with the parasites, the latter living within the cells unchanged and giving rise to no disturbance. If the parasite be destroyed phagocytosis may be regarded as a curative process. If the cell be killed by the parasite, or if the parasite continue to live in the body of its host, the process of phagocytosis is useless in preventing the spread of infection; there are cases (leprosy and to some extent tuberculosis) in which parasites find favorable conditions for development inside the cells, and finally cause their destruction. If the cells containing bacteria remain preserved for a length of time, they may wander with the enclosed bacteria to other parts of the body, in this way actually promoting infection.

Phagocytosis is therefore only of slight protective value in certain cases; yet it cannot be doubted that the phagocytes in other infections take up, not only dead or dying, but also living bacteria, and cause their death. The collection of great numbers of cells in the infected tissue may, through *close packing of the lymphatics,* offer *mechanical hindrance* to the spread of bacteria, yet the protection so afforded is frequently inadequate

If bacteria, either free or enclosed in cells, pass from the lymph-vessels into the **lymph-nodes,** the latter act as **filters,** as in the case of dust, and retain the bacteria; but the protection which they offer is sufficient only when the bacteria so collected are hindered in their reproduction or are killed by the influence of their surroundings. The destruction may be accomplished by phagocytosis, but *in many cases phagocytosis is possible only when the bacteria are weakened or have already been killed.* Further, the ingestion of living bacteria by the cells is not always followed by destruction, on the contrary, intracellular multiplication may occur.

More important than phagocytosis for the prevention of the spread of bacteria and other microparasites is the influence exerted by certain **chemical substances** in solution in the tissues. Since saprophytic, non-pathogenic bacteria, when injected into living tissue, are killed within a short time, we must assume that *in the tissues there are chemically active substances which are poisonous for many bacteria and cause their destruction.* Further, since some pathogenic bacteria increase only locally (tetanus-bacilli, diphtheria-bacilli, cholera-spirilla) and after a time perish within the infected area, without spreading through the body, it is probable that *the tissues contain* **substances which are likewise poisonous for pathogenic bacteria** and prevent their spread. The phenomena observed in local infections speak also for the fact that such substances at times are formed in increased amounts or are aided in their action by newly-formed substances. It is, furthermore, probable that the crowding of cells which takes place in the infected area or in its neighborhood contributes to such increase; nevertheless, attention should be drawn to the fact that in many infections the spread of bacteria comes to a standstill in places where there has been no crowding of cells. It is also a fact that in many infections the spread of bacteria is either wholly wanting (tetanus, diphtheria) or is insignificant. The explanation of this fact is to be sought, not so much in the assumption that local tissue-changes, through chemical substances or mechanical barriers hinder the entrance of bacteria into the lymph and blood, but that *there are present in the lymph and blood certain forces which are able to injure bacteria* actually taken into these fluids or to destroy them. (See paragraph on **opsonins**).

The **hostile action of the blood on bacteria** has been ascribed to the phagocytic action of the leucocytes; this theory is supported by the fact that such phagocytosis can be demonstrated in acquired infections or after the artificial introduction of bacteria into the blood; and by the fact that bacteria in the blood, enclosed in cells, may often be carried out of the vessels and deposited in different organs—the spleen, liver, bone-marrow, and kidneys—and destroyed or excreted. These observations do not warrant the conclusion that phagocytosis constitutes a protection against the spread of bacteria in the lymph and blood. Here, again, it is a secondary phenomenon which occurs when there are present in the blood bacteria or protozoa, that are not able to prevent themselves from being taken into the bodies of the leucocytes — that is, they exert a positive attraction on the phagocytes.

The forces which are able to hinder the development of bacteria in the *blood* are believed to depend on **antibacterial chemical substances,** which are designated **alexins** (Buchner). According to Buchner, with

whom the majority are in harmony, there is formed a ferment-like body, an **enzyme** (*cytase*) [Metschnikoff]), which, through the aid of an intermediate body (amboceptor), exerts its destructive action on the bacteria. *The leucocytes are probably the chief producers of this protective body,* and the leucocytosis observed in the course of many infections may therefore increase the protective power (see **opsonins** below).

So far as conclusions can be drawn from the behavior of the human and animal organisms in infectious diseases, we may assume *that in the blood of man there are always present protective chemical substances, that is, alexins,* particularly against bacteria which never or only exceptionally enter the blood; and *that others are produced only during the course of infection,* so that not until a certain stage of infection does inhibition of the development of the bacteria, through the formation of antibacterial substances, occur. In favor of such hypothesis is the fact that many bacteria (typhoid-bacilli, cholera-spirilla, pus-cocci) possess their full virulence when distributed through the body by the blood, but later suffer loss of virulence and finally die.

The **means of protection against the poisons produced in the tissues by bacteria** are to be found, first in rapid **excretion** by the kidneys, or by the stomach, intestine, and skin; this action may suffice to prevent fatal poisoning. Further, in certain infections in which true toxins are formed there is an antagonistic action in that the poisons are made ineffective through the action of **counter poisons,** so-called **antitoxins.** (See § 31 and § 32.)

The *antagonistic properties of blood and lymph* against certain bacteria have been demonstrated conclusively by experimental investigations. These experiments have shown that the bactericidal action of the blood of a given animal is exerted only on certain forms of bacteria and never on all; and that this action is subject to individual variations.

According to the investigations of *Fodor, Petruschky, Nuttal, Ogata, Buchner, Behring, Nissen, Pansini,* and others, the blood and the serum from dogs, rabbits, and white rats are capable of rendering the anthrax-bacillus harmless, and even of killing it; but this action is a limited one, so that after the introduction of a large number of bacilli into the blood taken from the vessels, the bacilli after a time begin to multiply. Defibrinated blood of dogs and rabbits can destroy the cholera-spirillum and typhoid bacillus; but, on the other hand, has no effect on the different pus-cocci, and against proteus; the same is also true with regard to the blood-serum. Human blood or blood-serum can kill typhoid-bacilli, diphtheria-bacilli, and the bacilli of glanders.

Von Baumgarten and *Walz,* as well as *A. Fischer,* oppose the view that there are chemically active substances in the blood, and explain the natural immunity of the tissues and the blood against certain bacteria as due to the inability of the bacteria to find there the necessary chemical conditions for growth and multiplication. They regard the fact that different bacteria which have passed into the blood or blood-serum do not develop at all, or show but partial or delayed growth and great diminution in numbers when cultivated on plates, as in no manner speaking for the presence of bactericidal substances in the blood. According to their view, the second transplantation into another culture-medium causes disturbance of the processes of assimilation and osmosis. There arise in consequence plasmolytic changes in the bacteria present in the serum; during the pouring of the plates the already injured cells die from disturbances of assimilation. On the other hand, it is to be noted that *A.* and *H. Kossel* have demonstrated that certain products of animal cells (nucleinic acid, protamine) possess bactericidal properties.

The **alexins** of the blood serum are made inactive through heating to 55° C., and are susceptible to the action of sunlight (*Buchner*), and can also be destroyed by living bacteria and their decomposition products. They resist pepsin. The addition of salt to the serum lowers their sensibility to heat. By means of a 90-

per-cent. sodium sulphate solution there may be obtained from dog serum a precipitate which remains active when dried at 70° C.

The **bactericidal action** finds its analogy in the **globulicidal** and **hæmolytic action** of the serum; that is, its capacity to destroy and dissolve the red blood-cells of an animal of a different species.

According to the investigations of *Ehrlich* and his students the **bactericidal** and **globulicidal antibodies** contain *two components,* one *thermolabile,* which is destroyed by heating to 55–60° C., and a *thermastabile,* which resists heating. Both must act together in order to bring about the death of bacteria or the solution of red blood-cells.

Ehrlich designates the thermostabile component as the *immune body* or *intermediate body* (*Bordet* "as the substance sensibilatrice"), the thermolabile as the *complement.* To the immune body he ascribes two *haptophorous side-chains,* one the cytophile, which unites with the cell (bacterial cell, red blood-cell), for which it possesses a chemical affinity, and a *complementophile,* which combines with the complement. It is therefore an *amboceptor,* which carries over the action of the complement to the cell. Buchner's *alexin* is identical with the thermolabile component, the complement of Ehrlich (*Bordet*). That a union of the immune body with red blood-cells and bacteria, respectively, does take place has been demonstrated by the investigations of *Ehrlich, Morgenroth, Hahn, Trommsdorff, von Dungern,* and others.

Hankin, Kanthack, Denys, Hahn, Löwit, and others assume, on the ground of experimental investigations, that the *alexins are produced by the leucocytes. Kossel* holds it as possible that the nucleinic acid present in the leucocytes in relatively rich amounts plays a rôle in the destruction of the bacteria. *Noesske* believes that the eosinophile cells of the bone-marrow in particular produce bactericidal substances. It is not possible at the present time to draw a definite conclusion as to the part played by the colorless cells of the blood in the defence against infections.

According to *Bitter, the bactericidal substance found in organs* — that derived from the lymph-nodes, spleen, and thymus — is to a certain extent different from that of the blood and the blood-serum, and therefore does not originate wholly in the blood. It is certain that the bactericidal action of the blood is not the only protective influence which can oppose the spread of an infection, or wholly prevent it, and confer immunity.

According to observations of *Czaplewski,* anthrax-bacilli in an infected organism, which have been taken into leucocytes, degenerate as a rule more slowly than those lying free in the blood and tissue-juices. It appears, therefore, as if under certain conditions the cells afford to the bacteria which they enclose a certain degree of protection from the bactericidal substances of the tissue-fluids.

The *antitoxins* which render the bacterial poisons harmless are usually formed during the course of the infection; but, according to the investigations of *Wassermann, Abel, Fischl, von Wunschheim,* and others, the serum of healthy men also contains such substances. Serum which contains the antitoxin against a certain toxin — for example, that against the diphtheria-toxin — can be a good culture-medium for the given bacteria; the antitoxin does not destroy the bacteria.

Animals refractory to diphtheria contain in the blood serum no diphtheria antitoxin, but according to *Wassermann* about 80 per cent. of human individuals have in their blood a not insignificant amount of antitoxin. The immunity of the animals depends therefore not on the presence of the antitoxin, but on a lack of affinity between the poison and the tissue-cells (*Ehrlich* and *Wassermann*). It is possible to produce in mice a fatal intoxication with the blood of apparently healthy fowls that have been injected with large doses of tetanus toxin.

Opsonins. The protective function of phagocytosis has been accorded a position of importance through the discovery by *Wright* and *Douglas* (1902) of the presence in the blood and other fluids of the body of certain substances, called *opsonins,* which render various bacteria susceptible to the phagocytic action of leucocytes. It is now an established fact that certain special substances, normal and immune, act on the bacteria and change them in such a manner that they are readily taken up by polynuclear leucocytes *in vitro.* Opsonins capable of acting on a variety of bacteria occur in normal blood. They appear to be important antibodies in infections with streptococci, staphylococci, pneumococci, micrococcus melitensis, gonococci, meningococci, the bacilli of plague, dysentery, anthrax, tuberculosis, typhoid fever, the colon bacillus, cholera spirillum, etc. Whether this wide range of opsonic action is dependent on a common opsonin or on a variety of specific opsonins is not yet determined. Specificity of the opsonins probably does not exist. Various researches suggest that they may be a constant quantity. They are to a

certain extent thermolabile, being partly destroyed at 60–65° C. Bacteria first treated with normal serum and then exposed to this temperature are taken up as under normal conditions. The opsonic power of the blood is increased in recovery from infection, and it can also be artificially increased by immunization with living attenuated bacteria, dead bacteria, or proteid constituents of the bacterial cells. The **opsonic index** is the relative influence of a patient's blood on phagocytosis as compared with that of normal individuals. It is determined by mixing in a capillary tube equal parts of the patient's serum, a suspension of leucocytes, and an emulsion of the bacteria against which the index is taken. Control tests are made in the same way with normal serum. The mixtures are incubated for a time, thin smears are made, dried, and stained, and the average number of bacteria taken up by the leucocytes is estimated. Regarding the index of the normal blood as unity, the average number of bacteria in the leucocytes of the patient's serum divided by it will be the opsonic index. 75–100 leucocytes are usually counted. A low opsonic index is taken as indicating the presence of an infection or of a low degree of resistance to it, while a high index indicates a high degree of resistance to a recovery from infection.

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§ 31. **The healing-powers of the body** *are those processes which are able to compensate for the changes caused by disease, and to render harmless or to remove any harmful agent that may still be present in the body. If portions of tissue have been destroyed, healing consists in removal of the dead tissue, and its replacement by new tissue.*

When the temperature of the body becomes abnormally low or high, compensation may be effected in such way that through regulation of heat-production and heat-dispersion the temperature is brought back to normal. If through trauma tissue is destroyed, the organism may repair the defect through the production of new tissue (*regeneration*) or by corresponding increase in similar tissues (*compensatory hypertrophy*).

If **poisons** enter the body and produce intoxication, healing follows only through rapid *excretion* of the poison, or its *destruction* or *neu-tralization* in the body; while at the same time the damaged tissues return to their normal state, existing defects being properly compensated.

In **infections** the *healing processes* follow directly on the *action of the protective forces;* indeed, the latter constitutes the first stage of healing; *the protective and healing processes are integral factors in repair.*

In many infectious diseases the influence of protective substances already present is supplemented by the **appearance of new substances foreign to the normal organism,** which as **bactericidal substances** and as **antitoxins,** respectively, antagonize infection and intoxication. The **bactericidal antibodies** are formed by the tissue-cells which through the infection have been placed under altered conditions of life; they spread through the tissues, and thus hinder the extension and multiplication of the bacteria. They are formed particularly in typhoid fever, cholera, and plague, and *show a certain specificity* in that they influence primarily those bacteria through whose vital activities they have arisen. This specificity is, however, not absolute, inasmuch as they can act on closely related species.

Antitoxins are formed in those infections in which toxins are produced. The action of the toxin takes place in this manner (Ehrlich): the poison molecule combines through a haptophorous side-chain with the haptophorous group of certain cells, while the toxophorous side-chain of the poison exerts its influence in a specific manner on the affected cells, so that we may regard the *antitoxins* as representing an excess of *haptophorous side-chains of the cell-substance susceptible to the*

poison, that are given off into the blood-serum, and combine the corresponding haptophorous side-chains of the toxins. The haptophorous group of the toxin is thus prevented from carrying over its toxophorous group to the cells and becoming active.

Toxin and antitoxin combine according to fixed quantitative relations.

Antitoxins are formed against the toxins of diphtheria and tetanus, pyocyaneus, ricin, and poisonous snakes, eels and mushrooms.

Since the antitoxins of snake-venom (*Calmette*) and that of the pyocyaneus toxin (*Wassermann*) are more easily destroyed than the poisons themselves, it is possible in a mixture of the two, when the combination has lasted but a short time, to destroy by heating to a certain degree the antitoxin alone, so that the toxin again becomes active.

The virulence of the toxin of diphtheria is weakened with age, through the fact that the toxophorous group in part becomes inactive.

According to investigations by *R. Pfeiffer,* confirmed by *Sobernheim, Dunbar, Loeffler,* and others, there is found in the blood-serum of animals made immune against typhoid-bacilli or cholera-spirilla, or of individuals suffering or convalescing from typhoid fever and cholera, a **specific bactericidal substance.** The addition of such serum to a virulent bouillon-culture of these bacteria so changes the latter that the bacteria when inoculated into the peritoneal cavity of an experimental animal rapidly disintegrate and are finally dissolved.

Bordet has shown that fresh human serum is also active in the test-tube outside of the human body. When heated to 56° C. this activity is lost (inactivation) but it may be restored through the addition of normal serum (reactivation).

Acording to the investigations of *Gruber, Durham, Pfeiffer, Kolle, Sobernheim, Widal, C. Fraenkel,* and others, the blood-serum of individuals ill, convalescing, or recovered from typhoid or cholera exerts a damaging influence on typhoid-bacilli or cholera-spirilla respectively; this influence being of such nature that in bouillon-cultures the bacteria so affected become motionless, clump, and are destroyed. When the serum is added to a hanging drop of bouillon-culture, the rapidly moving vibrios at once become motionless and collect in little heaps. *Gruber* believes that this phenomenon is to be explained by a swelling and bursting of the membrane of the bacterial cell, and assumes that this change enables the alexins to destroy the bacteria present in the body. He therefore designates the active substances in the serum *agglutinins,* and believes that to these may be attributed the chief agency in the healing of infectious diseases and in the production of immunity against the same. *Pfeiffer,* on the contrary, denies the occurrence of any swelling of the cell-membrane, and explains the phenomenon as the inhibition of development, and designates the active substances, the nature of which is wholly unknown, as *specific paralysins.* After *Gruber* had demonstrated the peculiar action of the blood-serum of typhoid-fever patients, *Widal (Sem. médicale,* Paris, 1896) proposed that this action of the blood-serum on cholera-spirilla and typhoid-bacilli respectively be utilized as a diagnostic aid. Numerous investigations have demonstrated that it is possible to make a diagnosis of typhoid from the action of the blood-serum on cultures of typhoid bacilli (*Widal's reaction*). (See § 33.) In fact the procedure is now carried out as a part of the routine diagnosis. It is to be remarked, however, that not every individual whose blood serum affects typhoid bacilli in this manner is suffering from typhoid fever, since the phenomenon may occur months or years after typhoid, and in those who have been vaccinated against the disease.

According to *Kraus,* there is present in the blood of animals artificially immunized against cholera and typhoid fever a body, which, on the addition of such a serum to a clear bacteria-free filtrate of cultures of cholera or typhoid bacilli, produces in the latter clouding and later precipitation, thus acting as a **precipitin.** (See § 33.)

The **protective substances** which appear in the blood in the course of infectious diseases are not always formed at the same place; in pneumonia they are said to be produced in the bone-marrow (*Wassermann*); in cholera and typhoid fever in the spleen (*Pfeiffer* and *Marx*); in "Rinderpest" in the liver (*Koch*). They are to be regarded as *specific secretory products* arising in response to specific stimuli.

The **bactericidal immune-bodies** are, according to their physical and chemical properties, to be regarded as *ferments* (they are neither globulins nor albumins), immune-bodies combined with the bacterial cells during bacteriolysis may be set free after the solution of the bacterial protoplasm, and again become capable of action.

It has often been assumed that the **fever** occurring in infectious diseases is a protective process favoring the destruction of bacteria; and it is not impossible that in *individual* cases it may exert such a favorable influence. For example, it is conceivable that a parasitic micro-organism, growing well at a temperature of 37–38° C. will not thrive at a temperature of 40–41° C., so that high temperatures in the course of fever may hinder its power of reproduction. The conclusion should not, however, be drawn from this that fever is a useful phenomenon which always favors the counterbalancing of pathological disturbances. Even in those cases in which the metabolic processes occurring during the fever exert an injurious influence on the bacteria, this is not to be taken as proving the usefulness of fever. We can only say that a part of the morbid processes occurring during an infectious fever leads to the formation of decomposition-products which may possess antibacterial or antitoxic properties.

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See also § 30, § 32, and § 33.

II.   The Acquisition of Immunity against Infection and Intoxication. Protection through Inoculation.

§ 32. The **acquisition of immunity against a particular infectious disease** is a phenomenon whose frequent occurrence has long been known through clinical observations.   This fact has been established chiefly by the observation that the great majority of men suffer but one attack of such widespread infections as measles, smallpox, whooping-cough, scarlet fever, and diphtheria, and that after such attack they are spared by the disease, even when they are again exposed to the danger of infection.   The knowledge of this fact is old, and early in the eighteenth century it led, in the Orient, to attempts to obtain immunity against the natural contagion of smallpox by the inoculation of material from smallpox pustules.   In the latter part of the eighteenth century Jenner discovered that the disease known as cowpox—i. e., a milder form of pox, which is an attenuated form of human smallpox—afforded protection against the true smallpox.   As a result of this observation, since the beginning of the year 1796, at first by Jenner himself, afterward by the physicians of all civilized countries, artificial inoculations of cowpox have been carried out on millions of human beings, with the result that through such inoculation a high degree of immunity against the true smallpox has been secured to the inoculated; so that at the present time, in all countires where vaccination is universally practised, the occurrence of widespread epidemics of smallpox, once so frequent, is rare, and the disease no longer assumes the character of a pestilence.

The investigations of the cause and origin of infectious diseases have shown that the **acquisition of immunity against a certain infectious disease through one attack** occurs in numerous infections, especially in those running an acute course; and represents sometimes a transitory, at other times a permanent peculiarity of the individual concerned; in pregnant women it may be transmitted to the fœtus *in utero*.   Observations have also shown that the single or repeated **inoculation of attenuated pathogenic bacteria**—that is, of bacteria which on account of slight virulence produce a disease that, in contrast to the infection with bacteria of full virulence, is relatively insignificant, often confined to a limited area—can also confer immunity against the corresponding disease.   Further, it has been demonstrated that the **injection of certain chemical substances produced by the bacteria** is sufficient to confer immunity against certain infections.

Immunity through the inoculation of attenuated specific disease-germs may be produced, for example, against anthrax, symptomatic anthrax, chicken-cholera, diphtheria, and swine-erysipelas.   The weakening of the virulence of bacteria may be produced either by the action of high temperatures or chemical agents, or by the action of the air alone; further, it may be produced by the inoculation of the bacteria into certain animals or through their long-continued cultivation on artificial media.   Inoculation is, in general, carried out by injecting subcutaneously first markedly attenuated, then less attenuated, and finally fully virulent bacteria together with their products.

According to the investigations of numerous authors, immunity in animals may also be produced by the **injection of sterilized cultures**

of bacteria—as, for example, against American hog-cholera, symptomatic anthrax, diphtheria, the infectious disease produced experimentally in rabbits by the injection of the *Bacillus pyocyaneus,* and the infection produced in guinea-pigs by cholera-spirilla.

A third form of artificial immunization, which Raynaud attempted as early as 1877, but was first securely established by Behring in 1890, can be produced by the injection into man or an experimental animal of **blood-serum taken from animals which were previously susceptible, but have been rendered immune by means of inoculations.** The most extensive and at the same time the most successful attempts thus far made have been carried out with *diphtheria* and *tetanus;* that is, in diseases in which intoxication through toxins forms the most striking feature. Moreover, successful experiments with the blood-serum of immunized animals, in cholera, swine-erysipelas, anthrax and typhoid fever, have been reported.

The specific protection which the blood-serum affords may be secured, not only by injection before infection occurs, but also after infection has taken place; so that the serum may be designated not only **protective.** but **healing.** For both protection against and for the cure of a certain infection a *definite amount of serum* is necessary, depending on the severity of the infection, and on the activity of the serum itself, the latter increasing with the completeness of the immunization of the originally susceptible animal furnishing the serum. If the serum is not injected until after infection has occurred, the amount must be greater in proportion to the lapse of time after the beginning of the infection.

In *diphtheria,* the injection of curative serum has been carried out in thousands of cases and its value has been shown beyond all doubt. In *tetanus* curative action of serum has been demonstrated in the case of experimental animals, guinea-pigs, and mice; but the results in man have not been altogether satisfactory. As a protective measure its injection before the actual onset of symptoms is of unquestioned value.

The blood-serum of immunized animals exerts its beneficial action, without doubt, through the presence of a *counter-poison,* an **antitoxin,** which neutralizes the poisons produced by the bacteria. In patients treated by a given antitoxin, there is produced an **immunity** against the corresponding bacterial poison—for example, against the poison produced by the diphtheria-bacilli, in patients injected with diphtheria-antitoxin.

Besides the antitoxins, the blood-serum of immunized animals or human beings may also contain **bactericidal substances,** which injure or kill the bacteria themselves; this is held to occur especially in cholera and typhoid fever.

In immunization by means of attenuated cultures or by sterilized bacterial products, the antibodies are produced as new substances in the organism; this process has been designated **active immurization** (Ehrlich); in the injection of immunizing serum the formed antitoxin is introduced from without; this is spoken of as **passive immunization.** It is probable that in the last case no new-formation of antitoxin occurs after the injection.

For the pioneer work in inoculation with attenuated cultures of bacilli cultivated outside the body, we are indebted to *Pasteur,* who, in 1880 demonstrated that chickens could be immunized against chicken-cholera through the inoculation

of cultures of *chicken-cholera bacilli,* that had been weakened through long exposure to the air.

Since that time numerous experiments have been carried out with other forms of bacteria, especially with attenuated cultures of the bacilli of anthrax and symptomatic anthrax. Good results have been obtained from inoculations against the symptomatic anthrax of cattle. Less favorable are the results in inoculations against anthrax, in that some of the animals die from the effects of the protective inoculation, while others are not rendered absolutely immune against a new anthrax infection.

Sheep and cattle may be made immune against *anthrax;* most expediently (*Koch*) by first inoculating them with attenuated cultures of anthrax-bacilli, which will kill mice but not guinea-pigs, and then with those which will kill guinea-pigs but not large rabbits.

As vaccine against *symptomatic anthrax,* there may be used cultures of the bacillus attenuated through heat or such chemical agents as sublimate solutions, thymol, eucalyptol, and silver nitrate; and by such inoculations cattle may be rendered immune. At the present time heat (*Hess, Kitt*) is most commonly used in the preparation of the vaccine. The infected muscle of an animal dying with symptomatic anthrax is chopped fine, triturated with one-half its weight of water, and pressed through a piece of linen cloth. Finally, the fluid is again filtered through a moistened piece of fine linen. The virulent material is then spread in thin layers on glass plates or flat dishes, and transferred to a dry chamber at a temperature of 32-35° C. When thoroughly dry the virus is scraped off and removed in the form of powder. When it is desired to give inoculations, the virus is triturated with double its weight of water and the fluid evaporated in a thermostat. By raising the temperature to 100° C. for six hours a weak vaccine is obtained; at a temperature of 85° C. for six hours a stronger one. For the immunization of cattle, about 0.5 gm. of the weaker virus in a dilute water solution is injected into the subcutaneous tissue of the animal's tail, and after eight to twelve days the stronger solution is similarly injected.

According to observations of *Chauveau* and others, protective inoculations may also be made by the injection of virulent bacteria in small quantities, or in such manner that the life of the animal shall not be endangered. In symptomatic anthrax this may be accomplished by the injection of small doses into the extremity of the animal's tail; such injections not causing fatal illness, but merely a local disturbance.

Cattle may also be immunized against *contagious pleuropneumonia* (*Schütz*) by injecting the tissue-juices from the lung of an animal dying from this disease into the tip of the tail. There is produced in this way a curcumscribed inflammation, or, at least, one which is confined to the tail; after recovery the animal is immune to both natural and artificial infection with this disease.

Hogs may be rendered immune against virulent bacilli of *swine-erysipelas* (*Pasteur*), by using, as vaccine, cultures attenuated by successive inoculations in rabbits. According to *Emmerich,* rabbits may also be made immune against the bacilli of swine-erysipelas through the injection into the ear-vein of a small quantity of a virulent bouillon-culture diluted with fifty times its volume of water.

Animals susceptible to *diphtheria* may be rendered *immune* against this disease, according to *Behring,* by the injection of cultures of diphtheria-bacilli which have been weakened in virulence by exposure for sixteen hours to iodine trichloride (1:500). Two cubic centimetres of such a culture are injected into the peritoneal cavity; after three weeks this injection is repeated with a diphtheria-culture (0.2 c.c.) which has been washed four days in bouillon containing iodine trichloride (1:5,500). After this, fully-virulent cultures are injected in increasing doses.

Protective inoculations against *rabies* were first carried out in cases resulting from bites by rabid animals, particularly in France (Pasteur Institute), Russia, and Italy. As inoculation-material, the spinal cord from rabbits which have been infected with rabies is used after it has been dried in air at a temperature of 23-25° C.; the virulence of the cord being gradually lost after about fifteen days. Small portions of a rabbit's cord thus treated are triturated in sterilized chicken-broth and injected subcutaneously into the bitten individual; at first pieces of cord greatly reduced in virulence are used, then those of gradually increasing virulence. According to the view held by *Pasteur,* the spinal cord contains both the microbes of the disease and the specific poison formed by them; if the latter spreads through the body more rapidly than the microbes, it confers an immunity against a subsequent spread of the microbes and affords protection to the nervous system in particular. In order to confer immunity it is, therefore, necessary to

introduce as large a quantity as possible of the chemical poison. According to the reports of the Institutes in which the Pasteur inoculations against hydrophobia have been carried out, it must be acknowledged that these inoculations have been success-ful in preventing cases of hydrophobia.

Immunity against *cholera* may be produced, in both man and animals (*Haffkine, Pfeiffer, Kolle, Voges,* and others) by the injection of sterilized or attenuated cul-tures of cholera-spirilla; this immunity (which is of short duration) depends on the formation of *specific bactericidal anti-bodies* in the blood (see Voges, l. c.). On the other hand, we do not yet possess a specific remedy by which the life of any animal or man infected with cholera may be saved.

Immunity against *typhoid fever* may be secured in man by the subcutaneous injection of sterilized cultures of typhoid-bacilli (*Pfeiffer, Kolle*); and the estab-lishment of the immunity may be recognized by the fact that the blood-serum of the individual so inoculated is found, after a few days, to contain *bactericidal sub-stances.* Attempts at immunization in cases already ill with typhoid (*Brieger, Was-sermann, C. Fraenkel*) have up to the present time been unsuccessful.

According to the reports published by *Koch* (*British Medical Journal,* 1897; *Deut. med. Wochen.,* 1897, No. 16; *Centralbatt f. Bakt.,* xii., p. 526) of the inves-tigations which were carried out during the winter of 1896–1897 with regard to the cattle-plague in Cape Colony, cattle may be immunized against "*Rinderpest*" by subcutaneous injections of 10 c.c. of the bile taken from animals dying of the disease; the condition of immunity becoming established at the latest by the tenth day. According to the report of Winkler ("Landwirthschaftl. Bezirks-Verein Giessen," August, 1900) hogs and cattle may be immunized against *foot-and-mouth disease* through feeding with milk of animals which are affected by the disease or have recently recovered from it. *Loeffler* and *Uhlenhuth* (*Centralblatt f. Bakt.,* xxix., 1901) have also reported successful protective inoculations with serum against the foot-and-mouth disease.

In the year 1890 *Koch* made the discovery that cultures of tubercle-bacilli con-tain an active substance, "*tuberculin,*" which, when injected into tuberculous in-dividuals, causes a rise of temperature and to some extent local inflammatory changes in the tuberculous foci. It was at first hoped that in tuberculin a remedy for tuberculosis had been found, but the many trials made with it on human beings and animals have shown that it indeed produces after repeated injections an im-munity against the toxic action of tuberculin, but does not hinder the multiplication of tubercule-bacilli and the consequent spread of the disease. Further, the local inflammation caused by the tuberculin leads to favorable results only under special conditions, but, on the other hand, often causes actual harm (through the meta-stasis of bacilli). Nevertheless, Koch's discovery has proved of great importance. In the first place, tuberculin is of practical value in the diagnosis of tuberculosis, in that injections excite fever. Inoculations for diagnostic purposes are now used extensively in cases of suspected tuberculosis in domestic animals. Moreover, the reports published by *Koch* gave a great stimulus to further investigations with regard to immunization by means of inoculation with bacterial toxins; and these investigations have led to the discovery of the antibodies of diphtheria, tetanus, cholera, and typhoid fever.

In 1897 *Koch* ("Ueber neue Tuberculinpräparate," *Deut. med. Woch.,* 1897) succeeded in obtaining from highly virulent cultures of tubercle-bacilli a substance which he claims is able to immunize against all of the constituents of the tubercle-bacillus. To obtain this substance young cultures of tubercle-bacilli are dried in a vacuum-exsiccator and then triturated. The product obtained by trituration is mixed with distilled water and centrifugated. The active substance is contained in the muddy precipitate thus obtained (designated by *Koch* as T. R.). This is again dried and triturated, dissolved in water to which twenty per cent of glycerin is added for the purpose of preservation. The fluid preparation contains 10 mgm. of solid substance in every cubic centimetre, and when it is to be used should be diluted with physiological salt solution. Through the use of large doses animals are said to become immunized in from two to three weeks. In the treatment of tuberculosis in man the dose should begin at $\frac{1}{500}$ mgm. and gradually be increased up to 20 mgm., the injections being given every other day. According to the observations so far published, the T. R. preparation does not appear to exert a curative action on tuberculosis in man.

The **blood-serum treatment of diphtheria,** i.e., the employment of the anti-toxins contained in the blood of an animal immunized against diphtheria as a means of curing that disease when it is already contracted, or as a protection against such infection, is a discovery which we owe to *Behring.* The favorable effects of the method have been affirmed by thousands of observations.

If culture-filtrates of the **tetanus-bacillus** are weakened by the action of chemical agents (iodine trichloride or iodine combined with potassium iodide), it is possible through repeated injections of such filtrates of increasing virulence to produce immunity in animals against tetanus (*Kitasato, Behring, Tizzoni, Buchner*). The blood of such immunized animals contains an *antitoxin which affords a sure protection to experimental animals against tetanus.* The antitoxin treatment of human beings suffering from tetanus has not given satisfactory results (see *Kohler* and *Schlesinger*, l.c.), not even in cases of relatively early injection of the antitoxin, though it is highly effective as a preventive measure.

Susceptible animals and human beings may be immunized against *bubonic plague* by means of sterilized cultures of the pest-bacillus (*Yersin, Haffkine, Kolle*); and it appears that in the blood-serum of immunized animals (the horse, for example) there are present anti-bodies which render the serum utilizable for both protective and curative purposes.

Animals may be made immune against *snake-poisons* by inoculations of small doses of such poison continued for some length of time (*Calmette, Tschistowitsch*); the blood-serum of such immunized animals is also found to possess an antitoxic action against the given poison, so that it may be used as a healing-serum. In Brazil, Mexico, Africa, etc., various methods involving the use of snake-poison itself are employed for the immunization of individuals against snake-bite, or for curing them after they have been bitten (*Brenning*).

According to investigations by *Ehrlich*, mice may be made immune against *ricin*, to which they are extremely susceptible, by mixing small doses of ricin with their food and injecting additional small doses subcutaneously. The appearance of the immunity occurs on the sixth day after the administration of the ricin, so on this day the animal can withstand a dose thirteen times as great as at the beginning. Through continued systematic inoculations the animal becomes immune to a dose eight hundredfold as strong. The immunity is produced by an antitoxic body, antiricin, which neutralizes the poison.

Vaccines. Since Wright's discovery of the opsonins, *bacterial vaccines* have been extensively employed in the treatment of certain infections. The vaccines are prepared by cultivating the given micro-organism on agar, suspending the growth in salt-solution, and heating to 65°–80° C. for an hour to kill the bacteria. The emulsion of dead bacteria is then injected. Immediately following the injection the opsonic index falls for a time, the so-called negative phase. This is followed in a day or two by a rise in the index to or above its original height, the positive phase. Considerable doubt has been thrown on the opsonic index as a guide in the progress of an infection; but many clinicians have obtained gratifying results in the treatment with bacterial vaccines. The conditions most amenable to this treatment are localized inflammations, notably acne, furunculosis, etc. As a method of treatment, its successful application is limited.

Attempts have been made to treat hyper-thyroidism with a specific serum (*Rogers, Beebe*). Experimental immunity to *Spirillum obermeieri* can be produced by the injection of filtered blood in which the spirilla have died out (*Novy*). Experimental immunity can be obtained in cerebrospinal meningitis (*Flexner*), and the therapeutic use of anti-meningococcic serum is a recognized procedure.

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See also §§ 30, 31, and 33.

III. The Active Substances of Acquired Immunity. Ehrlich's Side-chain Theory.

§ 33. **Acquired Immunity** depends on the presence of **specific antitoxic and bactericidal antibodies.** The process is seen in its simplest form in the production of antitoxins in diphtheria and tetanus.

According to the views of Ehrlich, only those substances are **poisons** that possess a chemical affinity for some element of the body and act through combination with this element. Congenital **immunity to poison** may, therefore, depend on the fact that the poison finds in the body no element with which it can react chemically, or if reaction occurs the body suffers no damage in a clinical sense. In **acquired immunity to poison** the **action of the toxin is prevented through the formation of an antitoxin.**

Complex **protoplasmic substances,** considered as chemical structures, consist of a *governing-nucleus* or *central-group* (*central ring*) and of various *side-chains* (Ehrlich). These side-chains combine with the side-chains of albuminous *nutritive* substances, and so bring about assimilation of the latter. Their significance is that of *receptors* or of a *haptophore group* which combines with a *haptophorous group* of the albuminous food-material. In the same way **toxins** *are anchored through their haptophorous group to the receptors of the cell-protoplasm, thus enabling the toxophorous group of the toxin to exert its action on the cell-protoplasm and to injure its vital functions.*

As the result of the combination of toxins with receptors, portions of the protoplasmic albumin-molecule are rendered incapable of function. If the life of the cell and its power of compensation are not damaged, there is produced only transient disturbance of the central group without definite injury to it; and the cell may again replace the side-chains and even form them in excess — throw them off, and give them to the blood. *Such detached side-chains or receptors constitute an* **antitoxin**. The *antitoxin* is, therefore, no new substance, but one normally present, which under certain conditions is produced in increased amount and given to the blood, and, circulating there, *combines the toxin to form a harmless body, and so prevent action on the cells.* The same substance in the living body, which *as a constituent of the cells* renders intoxication possible, becomes the cause of healing *when set free* in the blood-stream (von Behring).

The **bactericidal action of the blood-serum,** a phenomenon occurring in certain infectious diseases (typhoid fever, cholera, plague), is dependent on the *combined action of two substances.* One of these is a *ferment-like body* found particularly in the blood-serum of the normal organism. It is labile and is destroyed by heating to 55° C. Buchner has designated this substance **alexin,** Ehrlich **complement,** and Metschnikoff *cytase.* Alone it is not able to injure the bacteria, but needs for this action the coöperation of an **intermediate-body,** the **amboceptor** or **immune-body** of Ehrlich (substance sensibilatrice of Bordet).

The amboceptors are formed during the course of an infection, and are specific for that disease (specific immune-bodies), that is, they are active only in that disease in the course of which they are formed. They possess two haptophore groups, one of which (cytophile group) combines with a receptor of the bacterial protoplasm; the other (complementophile group) combines with a haptophore chain of the complement, so that the zymotic group of the latter can act on the bacterial cells. The amboceptor is less susceptible to heat than the complement and is not destroyed by heating to 60° C.

The **bactericidal sera** act, in the first place, in such way as to cause **death and solution of the bacteria,** in that the *specific immune-body,* the amboceptor, carries over to the bacteria the digestive action of the normal body-juices, in the complement, so that the bacteria are in part dissolved. Such sera contain, therefore, **bacteriolysins.** A second action is the phenomenon of **agglutination,** in that specific substances contained in the serum, **agglutinins,** combine with the bacterial cells and cause clumping. The agglutinins are less susceptible to heat than the lysins and are not changed at 56° C.

Finally, bactericidal immune-sera cause precipitation, in that certain substances contained in the serum, **precipitins,** or **coagulins,** form chemical combinations with certain substances given off from the disintegrating bacterial bodies and coagulate or precipitate them. If an active bactericidal serum be added to a clear fluid which contains such albuminous substances of the bacterial cells, there is produced a flocculent precipitate.

Precipitins withstand heating to 56° C. and may be dried without losing their potency

According to Ehrlich, the receptors for a toxin represent only a haptophorous group of cells with whose haptophorous chain the toxin has

combined. He designates the same as a *receptor of the I order*. On the other hand, the receptor of the cells for the nutritive albumin-molecules contains a haptophorous and a zymophorous group, the latter of which causes fermentative disintegretation of the anchored albumin-molecule. This is designated as a *receptor of the II order*. The receptor for bacteriolysin contains a haptophorous group for the anchoring of the ferment-like complement and a receptor for the combining of the disintegration products of bacteria, so that the former can act on the latter.

The receptors thrown off by the cells are designated by Ehrlich **haptins,** and he distinguishes: a *haptin of the I order*, the antitoxin, which combines the toxin to form a harmless body; *haptins of the II order,* the agglutinins, precipitins, or coagulins, which, after their union with the albumin of the bacteria, cause agglutination, coagulaton, and precipitation through the action of the zymophorous group; and *haptins of the III order,* or bacteriolysins, which as amboceptors carry over the fermentative action of the complement to the bacteria.

Under special conditions there appear, particularly in the blood, substances that act on the red blood-cells or tissue-cells or the soluble albumins of the human and animal organism in the same manner as the antibodies described above. According to their action they are classed as **hæmolysins** (globulicidal immune-sera), **cytolysins, precipitins,** and **agglutinins.** They arise when into the body of an animal there is introduced the blood, lymph, milk, or tissue from an animal of a different species (*Bordet, Tschistowitsch, Kraus, von Dungern, Wassermann, Ehrlich, Morgenroth, Landsteiner, Uhlenhuth,* and others). The blood-serum of a guinea-pig injected repeatedly with defibrinated rabbit's blood is able to dissolve quickly *in vitro* the red corpuscles of the rabbit, while normal guinea-pig's blood does not possess such power.

The action of **hæmolysins** or of a *globulicidal immune-serum* corresponds in all respects to that of the bacteriolysins, and the researches concerning the nature of the hæmolysins (*Ehrlich, Morgenroth*) have aided essentially in the explanation of the mechanism of bacteriolysis.

The immune-body or amboceptor appearing in globulicidal serum shows great specific affinity for the corresponding erythrocytes; it will combine with them at $0°$ C. and, when thus separated from the complement left in the serum, is not in itself able to dissolve the red blood-cells. The complement will not combine with the red cells without the immune-body. When the immune-body or amboceptor is present, the complement may, at a higher temperature, be carried by the amboceptor over to the red cells and cause their solution.

After intraperitoneal injections of laked blood of the same species, the so-called *isolysins* may be formed, that is, the blood-serum of the animal injected acquires the power of dissolving the red cells of another individual of the same species.

Cytolysins or *cytotoxins* arise through the injection of foreign cells into an organism, for example, after the injection of ciliated epithelium, spermatozoa, leucocytes, renal epithelium, adrenal cells, brain-substance, pancreas-cells, placenta-cells, and carcinoma-cells. In the case of ciliated epithelial cells and spermatozoa the action of the cytolysins contained in the serum can be recognized outside the body in the rapid cessation of movement (tricholysin, spermolysin).

Cytolysins act in the same manner as the hæmolysins.

Precipitins arise in the blood-serum as a specific reaction after the subcutaneous, intraperitoneal, or intravenous introduction of foreign albuminous substances.

A serum containing precipitins has the power, when added to the albumin solution used in the injections, of causing in the latter a precipitate. *R. Kraus* demonstrated this action for cholera-spirilla, that is, for the substance of the bacterial cell brought into solution. The serum of goats previously treated with injections of cholera-spirilla or with the bacterial substance causes a precipitate in filtrates of cholera-cultures that contain no bacilli. This property of the bacterial precipitins may be used in diagnosis.

According to the investigations of *Tschistowitsch, Bordet, Wassermann, Schütze, Ehrlich, Morgenroth, Myers, Uhlenhuth, von Dungern,* and others, such precipitins are also formed after the injection of foreign blood, milk, inflammatory

exudates, fresh and dried flesh, etc.; and through the aid of this method it becomes possible to distinguish from one another not only the red blood-cells of different species, but also flesh, milk, semen, etc.; that is, the precipitating serum of an animal A, that has been treated with an albumin of an animal B of another species, will precipitate the albumin of B, but not that of a third species.

This reaction of albumin obtained by biological methods (*biological method of differentiating albumins,* Wassermann and Schütze) is so extremely sensitive that the specific test for albumin is possible even at a dilution of 1:100,000. The precipitin reaction has found its most important application in the examination of *blood-stains,* but it is also of use in the differentiation of different kinds of meat, milk, etc., and can be applied also to the differentiation of plant-albumins.

The reaction is specific for the albumin of different species of animals and for man; between the albumins of different elements of the body, as, for example, between chicken-blood and the white of a chicken-egg, there exist only quantitative differences. An antiserum to human blood will precipitate urine containing albumin, purulent exudates, ascitic fluid, seminal fluid, etc.; so it may be inferred that the various fluids of the body contain the same receptors as those of the blood-serum. In the examination of spots, stains, etc., the first thing to be determined is the presence of blood (guaiacum test, Teichmann's test, spectroscopic examination). When this is determined, the biological test, properly handled, gives certain results, particularly when the animal used for the production of the serum is not closely related. An antiserum for human blood gives only a weak reaction with ape's blood (particularly that of anthropoid apes); and similar conditions exist between the horse and the donkey, and between the chicken and pigeon.

For the demonstration of the presence of human blood or albumin, the serum of rabbits properly treated beforehand may be used to best advantage, but that of the horse, sheep, or goat may also be employed (according to *von Dungern,* cold-blooded animals produce no precipitins). To produce the antiserum (*Uhlenhuth*) 5–10 c.c. of a dilute solution of albumin derived from human tissues or blood are injected into a rabbit at intervals of several days, until a test of blood taken from the vein of the ear, made about five days after the last injection, shows the serum to be active. It is strange that the time in which this change in the serum occurs varies greatly with individual animals. When the serum has attained its full strength, the animal is anæsthetized, the thorax opened, and a cut made into the heart. The blood is taken up by a pipette and collected in a sterilized glass graduate. The serum when separated is filtered through a Berkefeld filter and when ready for use must be perfectly clear. The albuminous material to be tested is dissolved in physiological salt-solution.

A serum of high potency may contain precipitins that act not only on homologous albumins, but also on heterologous. *Uhlenhuth* recommends, therefore, a marked dilution (1:1,000) of the fluid to be examined, which, moreover, must be perfectly clear. To 2.0 c.c. of the dilute fluid 0.1 c.c. of the antiserum is added, and in the presence of homologous albumin a cloudy precipitate forms at once or after one or two minutes.

Agglutinins that cause clumping through their functional molecule-groups may be combined first with bacteria, but also after that with red blood-cells. Agglutinable substances and agglutinins possess specific combining haptophore-groups (*Eisenberg* and *Volk, Wassermann*). In the agglutinable substance the functional group is more labile and more easily destroyed than the haptophore-group; this is true also of the agglutinin (*Wassermann*). Through external influences the functional group may be lost, and from the agglutinin there is produced an agglutinoid, which is no longer able to cause agglutination, and through its combination with the agglutinable substance is able to prevent the occurrence of agglutination in the presence of agglutinin. As has been mentioned above (§ 31), agglutination has been observed chiefly in the case of cholera-spirilla, typhoid-bacilli, pyocyaneus, colon, and tubercle bacilli.

Immune-agglutinins are produced during the process of immunization by increased formation and liberation of groups that under certain conditions occur in slight amount even in normal serum.

Agglutination can be applied to the diagnosis of a given disease, but it must be remembered that the serum of healthy individuals causes agglutination (in typhoid fever even in dilutions of 1:20, while the serum of persons having the disease will agglutinate at a dilution of 1:50); and that a serum can also agglutinate to a greater or less degree other bacteria than the one coming under the influence of its agglutination power. The serum of typhoid patients or of those immune to typhoid acts on many colon-species even in high dilutions.

The precipitable substance in culture-fluids is, according to Wassermann, identical with the agglutinable substance in the bacterial cells; that is, the substance present in the uninjured bacterial cells, combining in agglutination with the agglutinating serum, is, in the culture-fluids, dissolved out of the bacteria, set free in the same, and gives there a specific precipitate with the serum.

Agglutination and dissolution of bacteria, according to *Wassermann, Ehrlich, Morgenroth,* etc., are not caused by the same substance, as is believed by *von Baumgarten* and *Gruber* to be the case. Agglutinins and amboceptors or immune-bodies are distinct from each other and do not have the same haptophorous group in common. The immune-body needs for its action the complement, the agglutinin does not.

The agglutinin is made up of separate or partial agglutinins, and a bacterial agglutinin may, therefore, vary in its constitution according to the biological qualities of the animals in which it is produced. Two varieties of bacteria (typhoid-fever and colon-bacilli) may also possess a number of partial agglutinins in common. It, therefore, becomes necessary (*Wassermann*), when applying agglutination-tests for the purpose of diagnosis, to work always with such dilutions as possess a limit of action not far from that obtained by titration for the given bacterial species (the limits of potency of any serum may vary greatly). A positive agglutination is, therefore, decisive as pertaining to that species with which the animal producing the serum was previously treated.

The **production of antitoxin** plays the most important rôle in the healing of diphtheria and tetanus; the success attending the prophylactic and therapeutic use of these antitoxins has already been mentioned in § 32. The toxin is not destroyed by the antitoxin. When snake-venom (*Calmette*) is mixed with antitoxin so that the mixture becomes harmless to animals, and if the more thermolabile antitoxin be destroyed by heating to 68° C., the mixture again becomes poisonous. The same thing may be demonstrated in the case of the toxin and antitoxin of the Bac. pyocyaneus.

According to *Wassermann,* the substance of the central nervous system chiefly affected by tetanus is able to combine with the tetanus toxin after the manner of an antitoxin and so render it harmless. Tetanus toxin rubbed up with the brain substance of a normal rabbit becomes so weakened that guinea-pigs can bear ten times the fatal dose without damage. According to *Ransom,* the tetanus-poison injected in fatal doses into pigeons is demonstrable in all organs except the central nervous system, with which it has entered into chemical combination.

Therapeutic attempts with **bactericidal sera** have not given such good results as those of antitoxic sera. In the first place, the bactericidal sera have no influence on an existing intoxication. Further, action on the bacteria present is impossible when the injected serum finds no free complement in the blood of the patient or when the amboceptor from animal blood (horse blood) does not combine with the complement of human blood.

The agglutinins, precipitins, etc., can in turn produce in the organism anti-anti-bodies, antiagglutinins, antipreciptinins, etc.

Hypersusceptibility or **anaphylaxis.** Animals may react to certain toxic or foreign substances in one of two ways, either by increased resistance or immunity or by increased susceptibility (hypersusceptibility or anaphylaxis). According to *Theobald Smith, Otto, Rosenau* and *Anderson, Gay* and *Southard,* etc., there occurs a remarkable toxic action in guinea-pigs as the result of an injection of a small dose of horse-serum (.0001-.1 c.c.), followed after ten days or two weeks by a second injection of relatively large amount (5 c.c.), the reaction being characterized by severe symptoms and death within one hour. This reaction is specific in that guinea-pigs sensitized with horse-serum do not react to the second injection of other proteid substances, and *vice versa.* The reaction following a second injection of the same proteid in guinea-pigs appears to be common to all higher forms of albuminous substances (white of egg, hæmoglobin, milk, extract of peas, bacterial proteids, etc.). Simpler albuminous substances, such as peptone, seem to have slight sensitizing and poisonous properties, while lower nitrogenous compounds as leucin and tyrosin possess none at all. Hypersusceptibility in the guinea-pig may be transmitted by the female to the offspring. The hypersusceptibility may persist for a long time (*Rosenau* and *Anderson*). The hypersusceptibility produced in guinea-pigs to second injections of bacterial proteids resembles that produced by second injections of horse-serum. It is significant that the period of incubation in a number of infectious diseases corresponds to the ten or fourteen days required to sensitize animals to a foreign proteid. (For literature see *Anderson* and *Rosenau, Jour. of Med. Res.,* July, 1908.)

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CHAPTER IV.

Disturbances in the Circulation of the Blood and of the Lymph.

§ 34. The mass of blood is kept in motion by the rhythmical contractions of the heart. The blood, as it is driven into the elastic aorta toward the periphery of the body, meets a significant degree of resistance, caused by the friction in the innumerable divisions and subdivisons of the arterial system. This resistance occasions a relatively high pressure throughout the arterial system, which in the human femoral artery equals that of about 120 mm. of mercury. After passing through the capillaries the blood arrives in the veins with little velocity, and stands in the veins under slight pressure, which varies according to the location of the vein, and is greatest where a high column of blood rests on the lumen of the vein. In the great venous trunks of the thorax the pressure is usually negative, especially during inspiration, as the thorax during this stage of respiration aspirates the blood from the veins outside the chest. Only during forced expiration does the positive pressure in the veins rise somewhat higher.

Assuming the mass of the blood to be constant, the degree of pressure *in the aorta,* at any given moment, is dependent on the work of the heart and the resistance in the arterial system. The latter in turn is dependent on the variations in the total diameter of the combined cross-sections of the blood-vessels, brought about by the elasticity and contractility of the arteries. In the major circulation the arterial tone is pronounced; in the lesser circulation it is slight, the blood-pressure in the pulmonary artery being only from one-third to two-fifths that in the aorta. Both the heart and the arteries are under the influence of the nervous system, which regulates their activity.

The activity of the heart consists in rhythmical contractions of its musculature; and its efficiency presupposes that the heart-muscle, and the cardiac ganglia, are sound. Every disease of the heart, therefore, in so far as it diminishes the contractile capacity of the heart-muscle and lessens the activity of the ganglion-cells, and in so far as lessened functional activity of the cardiac muscle is not compensated by increased activity of other parts, will **diminish the functional capacity of the heart.**

In many cases in which the functional capacity of the heart-muscle is impaired, anatomical changes, such as fatty degeneration and necrosis of its cells, can be demonstrated; in other cases no anatomical changes can be made out, especially in those cases in which diminution of working-capacity follows exhaustion caused by overexertion. This may occur when the heart is forced to work for some time slightly above the normal, but under unfavorable conditions, as, for example, in elevation of the body-temperature; as well as in cases when for a short period it is overworked to an excessive degree. Under certain conditions disturbances of nutrition and intoxications, such as occur in the infectious fevers, as well as sudden diminution in blood-supply from obstruction of a coronary

artery, may cause insufficiency of the heart within so short a time that the heart-muscle presents no recognizable anatomical lesion. The work of the heart may also be made difficult through the formation of adhesions between the epicardium and pericardium, and between the latter and the contiguous pleura, in consequence of which the contractions of the heart are hindered.

Through the collection of fluid in the pericardial sac in the course of certain diseases, through deformities of the thorax marked by abnormal smallness of the thoracic cavity, and through a high position of the diaphragm, the diastolic dilatation of the heart and the free afflux of blood from the veins may be hindered to such an extent that the ventricles receive too little blood. If, following pathological processes in the heart-valves, there result rents or distortions of the flaps or adhesions between them, or if in case of dilatation of the heart and of the valvular orifices the valve-flaps become too short, there may arise those conditions of the auricular and ventricular orifices known as insufficiency and stenosis. The former condition is characterized by failure of a valve to close completely during the diastole of the auricle or ventricle lying behind the given valve; the second condition, by the fact that during the contraction of the auricle or ventricle the valvular orifice does not suffice for the free passage of blood through the opening. The effect of stenosis is that of opposing additional obstacles to the outflow of the blood during systole. In aortic and pulmonary insufficiency the blood regurgitates, during ventricular diastole, from the great vessels into the ventricles; in mitral and tricuspid insufficiency the systole of the ventricle causes regurgitation into the corresponding auricle.

Finally, there are not infrequently formed in the heart masses of coagula, which, if they lie near the orifices may interfere with the proper closing of the valves, or cause narrowing of the ostium.

As a result of the above-mentioned pathological conditions, the **efficiency** of the **heart's function is impaired,** so that in a given time too little blood passes into the arterial system, the aortic pressure falls, and the velocity of the blood-current is diminished; while in the venous system the blood collects, and the venous pressure rises. There is consequently *inadequate filling of the arteries* throughout the body, varying, indeed, according to the degree of contraction in individual arterial systems, while both veins and capillaries are, on the other hand, overfilled with blood. There develops, therefore, a condition of general **venous hyperæmia,** which in some parts may become so marked that the tissue, because of the engorgement of the capillaries with venous blood, acquires a *blue-red, cyanotic appearance.* When the difference in pressure between the arterial and venous systems becomes reduced to a minimum, the circulation comes to a standstill, while the right side of the heart becomes distended with blood.

Should the contractions of the heart from any cause become weak, the pulse-wave also becomes small. If the rate of the heart-beat is diminished in frequency, the arterial system empties itself to a greater extent than normally during the pause between the systoles.

If the impairment of cardiac efficiency involves the left heart, as is the case, for instance, in valvular disease of the left side, the disturbance of circulation is manifest first in the systemic arteries, as well as in the pulmonary vessels.

In stenosis of the aortic valves, the arteries, if the heart's action remain unchanged, fill slowly and incompletely (pulsus tardus). In aortic insufficiency a normal or even an increased amount of blood is thrown into the arteries during systole (pulsus celer), but a part of this flows back during diastole. In both cases the left ventricle becomes distended, the emptying of the left auricle is hindered, its cavity becomes dilated, and finally the blood is backed into the pulmonary veins. Owing, however, to the low pressure in the pulmonary circulation, the blood is readily dammed back on the right ventricle, and the blood stasis may finally extend into the right auricle and the systemic veins.

Valvular lesions at the mitral orifice produce similar effects on those portions of the circulatory apparatus lying behind the left auricle; in such cases there is also produced a condition of pulmonary stasis, with rise of pressure in the pulmonary arteries and veins; while the left ventricle either receives too little blood (stenosis) or during its contraction drives a portion back into the auricle (insufficiency).

In valvular lesions of the orifices of the right heart the damming back of the blood is limited to the veins of the systemic circulation, while in the pulmonary circulation both pressure and velocity are diminished. Further, the pressure in the aorta falls, since the left side of the heart receives too little blood.

The damming back of blood in the great systemic veins may manifest itself by *venous pulsations* in the neighborhood of the thorax, inasmuch as retrograde waves proceeding from the heart pass through the veins toward the capillaries, distending the veins to such an extent that the valves, particularly those of the jugular bulb, are rendered inadequate. In these circumstances, therefore, the essential cause of the transmission of venous pulsation is insufficiency of the venous valves. In the event of imperfect function of the valve in the jugular bulb, slight pulsation may be observed even during normal action of the heart; but when the veins are distended, and particularly in the case of tricuspid insufficiency, the pulsation becomes much stronger and extends further toward the periphery. If the tricuspid is adequate the venous pulsation (presystolic) is only the expression of the rhythmical occurrence of a hindrance to the outflow of blood from the veins (negative or normal venous pulse). In tricuspid insufficiency the contraction of the right ventricle forces blood back through the tricuspid opening into the right auricle and into the veins beyond, giving rise to systolic venous pulsation (positive venous pulse).

If, in a heart affected with a valvular lesion, the chambers lying behind the lesion become distended with blood, the muscular walls of these chambers, if otherwise normal, may by increased activity **compensate for the valvular lesion** within certain limits. In the course of time there results an increase in the volume of the heart-muscle, **hypertrophy,** which enables the heart to carry on its increased work for a prolonged period. Such compensation frequently becomes inadequate, with the result that the aortic pressure is permanently lowered, while the venous pressure, on the other hand, is abnormally high. There is, at the same time, the danger that the heart-muscle may in time become exhausted, or that even a slight illness may render the heart insufficient. Thus, prolonged quickening of the heart's rate, by shortening the diastolic periods of rest, may cause exhaustion and insufficiency. Arrest of the

heart's action finally follows, with great accumulation of blood in the heart, since the heart is no longer able to drive onward the mass of blood entering it.

Increase of the heart's action — that is, increase in the frequency of its contractions, these at the same time remaining strong and complete — causes an increase in arterial pressure and in the velocity of the blood-current. When increased demands are frequently made on the left side of the heart — as happens in heavy bodily labor, conditions of luxurious living, abnormal irritability of the cardiac nerves, etc.— the left ventricle may become hypertrophic and act with greater force. Inasmuch as quickening of the blood-stream causes the right heart to receive a greater amount of blood during diastole, hypertrophy of the right ventricle is usually found in connection with the hypertrophy of the left.

Lessening in the mass of blood or **general anæmia** from loss of blood leads temporarily to a fall of pressure in the aorta; but if the loss of blood be not excessive, the pressure rises again, as the vessels adapt themselves to the changed conditions, and, as the result of stimulation of the vasomotor centre through local anæmia, show a greater degree of contraction. Under normal conditions the mass of blood is quickly increased through the absorption of fluids, and later by regeneration of the blood. Similarly, in **anhydræmia** — i.e., a diminution of the water of the blood — the arterial pressure is lowered and the blood-current slowed. After severe hæmorrhages the arterial pressure is lowered for a greater length of time, the circulation is slowed, and the pulse, because of the lessened stimulation of the vagus-centre (Cohnheim), is frequent and small.

In permanent diminution of the blood-mass — i.e., the condition known as **chronic anæmia,** which occurs under varying conditions — the vascular system is imperfectly filled, the blood-pressure lowered, and the blood-current slowed. Both heart and blood-vessels adapt themselves to the new conditions and become diminished in volume. In the case of marked deficiency of hæmoglobin, degenerations of the heart-muscle, particularly fatty degeneration, frequently occur.

Increase in the mass of the blood, through the injection of blood or salt-solution into the vessels, is followed in animals by temporary increase in pressure and in the velocity of the blood-current. Return to the normal is brought about, partly by dilatation of a sector of the vascular system, particularly in the abdomen, and partly through elimination of the surplus from the vessels. If the mass of blood comes to stand in abnormally high proportion to the body-weight, if there exists a **permanent plethora,** the pressure in the aorta becomes permanently raised, the work of the heart is increased, and a corresponding *hypertrophy of the heart develops.*

When the arterial blood-pressure is raised there occurs an increased giving-off of fluid from the blood, and thereby a concentration and diminution in the amount of the venous blood; in lowering of the blood-pressure the amount of fluid given off is diminished and eventually an increased taking-up of fluid occurs. This change in the venous blood is, under normal conditions, compensated for in the lungs: in the first case, through taking-up of lymph from the lymphatics; in the second case, through giving-off of lymph to the lymphatics (*Hess:* " Beeinflussung des Flüssigkeitsaustausches zwischen Blut u. Geweben durch Schwankungen des Blutdruckes." *D. Arch. f. klin. Med.,* Bd. 79, 1903).

§ 35. **Increase of the general vascular resistance** may occur in either the greater or the lesser circulation, and results in increased pressure behind the point of increased resistance, and diminished pressure beyond it.

In the **systemic circulation** the hindrance may lie either in the main vessel, the aorta, or in the arterial branches, whose degree of contraction maintains and governs the normal pressure in the aorta. Vascular contraction involving a great number of arteries and their branches, and sufficiently well marked to increase the blood pressure, is generally a temporary phenomenon, passing off with relaxation of the arterial tension. Nevertheless, permanent increase in the aortic pressure with consequent hypertrophy of the left ventricle does occur; and this cannot be explained otherwise than as the result of the contraction of the lumen of the smaller arteries. Transitory arterial contraction and increase of pressure occur particularly through increase in the amount of carbonic acid in the blood. Permanent increase in aortic pressure is, on the other hand, a result of chronic disease of the kidney, in which the secreting parenchyma is destroyed. Inasmuch as the portion of the vascular system which is thus cut off is much too small to cause such an increase of pressure throughout the whole aortic system, and since the vessels leading to other organs might become correspondingly dilated, it must be assumed that in the case of contracted kidney some other hindrance to the circulation occurs in more extensive vascular areas. This hindrance would most naturally be sought in the apparatus which normally serves to keep the aortic pressure at its proper height, namely, in the smaller arteries of the body. Whether the condition is caused by nervous stimuli arising in the kidney, or by the action of retained urinary or other chemical substances on the vasomotor centres or directly on the vessel-walls, or whether the heart is excited by nervous stimuli to increased action, we are not at present able to say.

Increase of resistance in the aorta may result from stenosis of this vessel, as occurs in rare cases at the isthmus, or from congenital narrowing of the whole aorta, from large aortic thrombi, or from extensive disease of the vessel-wall, in consequence of which the intima is rough and nodular, the entire vessel rigid, inelastic, and unyielding; or, finally, from dilatation of the vessel, whereby eddies are formed in the blood-stream.

Lowering of resistance in the systemic circulation is possible through relaxation of the tone of a large part of the arteries, and this may happen when the vasomotor centre is paralyzed, or when the cervical cord is divided or partly destroyed. Since the blood, in this case, flows abnormally quickly from the arteries into the veins, the difference in blood-pressure between the arteries and veins is lessened, the current becomes slower, the heart receives too little blood during diastole, and, finally, the circulation may come to a standstill.

Increase of resistance in the pulmonary circulation occurs most frequently as the result of disease of the lungs and pleura. Adhesions of the pleura, as well as spinal curvatures, which interfere with the expansion of the lungs and their change of volume during inspiration, thus depriving the circulation of an efficient aid, may cause such increase in pulmonary resistance. Of great influence, moreover, are such affections of the lungs as emphysema, retraction and induration or destruction of

lung tissue — all of which lead to the obliteration of pulmonary capillaries; compression of the lung through pleural exudate; and, finally, compression of the pulmonary arteries by aortic aneurism or by tumors.

If the hindrance is only slight, the blood, by collateral channels may make a new passage to the left heart without any increase of pressure; the rate of the current in the blood-vessels which are unobstructed alone being increased. Greater obstacles cause increase of pressure in the pulmonary artery and the right heart, and if the condition persists for some time the right ventricle through increased exertion may become hypertrophic. This occurs, however, only when the heart-muscle is adequately nourished and when the mass of the blood is not diminished to correspond to the diminution of the area of the pulmonary vessels. If the right heart is not able to overcome the obstacles in the pulmonary circulation, the blood is dammed back on the right heart, and eventually into the systemic veins.

Increase of the pressure in the right side of the thorax hinders the entrance of venous blood into the right heart, and causes the accumulation of blood in the systemic veins. Sudden increase of pressure may cause retrograde flow of blood into the neighboring veins.

The observation that hypertrophy of the heart follows different diseases of the kidneys has been interpreted in various ways. Some writers seek the cause in an increase of the volume of the blood (*Traube, Bamberger*), others (*Senator, Ewald*) believe it to be due to the changed character of the blood, while others (*Gull* and *Sutton*) ascribe it to widespread change in the walls of the small arteries. According to the investigations made up to the present time, there can be no doubt that the hypertrophy of the heart in diseases of the kidney is dependent on an increase of aortic pressure. This increase is best explained by increase of the resistance in the small arteries of the entire body, due to the contraction of the small arteries. This contraction must be brought about either through the direct action of urinary substances contained in the blood or by some reflex stimulus from the kidneys, or finally by some influence exerted on the vasomotor centre. It is possible that the heart also may be excited to increased activity.

II.   Local Hyperæmia and Local Anæmia.

§ 36. To the blood is assigned the function of supplying all the organs and tissues of the body with nourishment. The cells of which the various tissues are composed are able to maintain their existence without the advent of fresh nutritive material only for a short time; for this reason the majority of the tissues are supplied with blood-vessels, and those not possessing vessels of their own are placed in intimate connection with vascular structures.

The demands of the different tissues for blood are not always the same, and there is consequently a corresponding increase or decrease in the amount of blood contained within an organ or tissue at any given moment. An organ rich in blood is designated **hyperæmic;** one poor in blood as **anæmic.**

The regulation of the amount of blood which an organ receives under physiological conditions is brought about by a change in the resistance in the afferent arteries; this is effected entirely through variation in the calibre of the arteries. Since the total mass of blood in the body is not sufficient to fill all the vessels at the same time, an extra supply of blood to one organ is possible only by supplying a less amount to other parts. The change in the calibre of an artery is determined, aside from the blood-pressure, by the elasticity of its wall and the degree of contraction

of its muscle-fibres. These fibres are the regulating element; their activity is dependent partly on influences affecting them directly, and partly on nervous influences from the intramural plexuses and from the vasomotor centres in the medulla oblongata and the spinal cord, some of these stimulating, others inhibiting muscular action.

When the departures from the average blood-supply of any part of the body overstep the physiological limits, or if such variations arise without physiological causes, or are unduly prolonged, the condition is spoken of as **pathological hyperæmia** and **pathological anæmia**. These conditions are brought about by the same regulating mechanism as that which governs the normal blood-supply.

Hyperæmia of an organ is caused **under pathological conditions** either by increase in the arterial supply or through obstruction and damming-back of the venous out-flow; there are distinguished, accordingly, two forms, *active* or *congestive (arterial) hyperæmia* and *passive* or *stagnation (venous) hyperæmia*. **Active hyperæmia** arises through *increase of the afflux of blood (congestion)*, and may be *idiopathic* or *collateral*. The first of these plays the more important rôle. It depends on relaxation of the muscular tunics of the artery, which may be brought about either by paralysis of the *vaso-constrictors (neuroparalytic congestion)*, or through *stimulation of the vaso-dilators (neurotic congestion)*, or through direct *weakening* and *paralysis of the muscles* (as, for instance, by heat, bruising, action of atropine, brief interruptions of the blood-current), or, finally, through *diminution of the external pressure exerted on the vessels*. *Collateral hyperæmia* is merely the result of diminished flow of blood to other parts. It occurs first in the immediate neighborhood of the parts whose blood-supply is lessened; later, the blood may be driven to such other and more distant organs as require it.

Active hyperæmia is characterized by more or less *redness* and *swelling*, which are striking in tissues rich in blood-vessels. The blood flows through the widened channels with increased velocity, and gives to the tissue the color of arterial blood. Superficial tissues which, because of their exposure, are slightly cooler than the deeper viscera, become, as a result of increased blood supply, warmer than those neighboring tissues which are less richly supplied.

Passive Hyperæmia arises through *retardation* or *obstruction of the flow of blood from the veins*. *General passive congestion of the systemic veins* occurs in those cases in which, through weakness of the heart's action, valvular insufficiency or stenosis, or obstructions to the pulmonary circulation, the emptying of the large veins into the right heart is hindered. In the pulmonary circulation stagnation of the blood-stream may be brought about by any cause hindering the outflow of blood from the lungs, particularly valvular lesions of the left heart, weakness of the left side of the heart, and, more rarely, obstructions in the systemic arteries. Not infrequently stasis of the pulmonary circulation may reach such a degree that the blood is dammed back into the right heart, and into the veins of the systemic circulation (see §§ 34 and 35).

Local passive congestion may depend directly on the fact that the progress of blood through the veins is not adequately supported by the activity of the muscles and the aspiration of blood from the veins during inspiratory enlargement of the thorax. The absence of the first factor is apparent in the branches of the inferior vena cava; for example,

in individuals who pass a large part of their time sitting or standing without active bodily exercise, so that the emptying of the deep-seated venous branches into the vena cava is dependent almost wholly on the activity of the vein-walls, which by virtue of their elasticity work against the pressure of the column of blood resting on them. The absence of aspiration of venous blood may, on the other hand, make itself felt in disturbance of inspiration through inflammation or other disease of the lungs or pleura.

A further cause of local passive hyperæmia consists in the narrowing or closing of individual veins, as in compression, ligation, formation of thrombi (§ 38), and invasion of the veins by new-growths. For example, the pregnant uterus may compress the pelvic veins, a thrombus may obstruct the cerebral sinuses or the femoral or portal veins, or a malignant tumor of the pelvis may grow into the pelvic veins.

When through any of the above-mentioned processes, single veins become occluded, the effect is often negligible, inasmuch as the veins concerned may possess free communication with other veins, so that but slight obstruction is offered to the outflow of the blood. If, on the other hand, the occluded vein possesses no collateral communications, or small ones which are inadequate for the passage of blood — as is the case with the main divisions of the portal vein, the sinus of the dura mater, the femoral and renal veins — there results more or less marked passive congestion in the area drained by the vein in question.

The effect of an obstacle to the outflow of blood shows itself first in that portion of the vein lying between the obstruction and the periphery, the blood-current becoming slowed or checked entirely, while at the same time there follows progressive dilatation of the veins through the continued afflux of blood from the capillaries. If through the effect of the elastic and contractile vein-walls the obstacle is overcome, the circulation is maintained, and the blood flows toward the heart through those channels which it still finds open. Not infrequently the small veins thus called on to perform increased labor become gradually dilated. When the obstacle cannot be overcome and communicating vessels capable of dilatation are not present, the circulation comes to a standstill, and thrombosis may be (§ 38) produced in the obstructed vessel and its tributaries.

If congestion in a venous area extends to the capillaries, so that they become overfilled with blood, the affected tissue becomes *blue-red* or *cyanotic*, exhibiting at the same time a certain degree of *swelling*.

Both active and passive hyperæmia, observed during life, may, after death, show a different appearance, and not infrequently disappear entirely. This is especially the case in the active hyperæmias of the skin, also in those of the mucous membranes. This is dependent on the fact that the tissues, put on the stretch by dilatation of the capillaries, contract on the latter, after the stoppage of the circulation, and by counter-pressure drive the blood from the capillaries into the veins. In this way a tissue which was red during life may become pale after death. On the other hand, tissues which during life were pale or at least showed no special redness, may after death take on a blue-red color. This takes place particularly on the sides and back of the trunk (in those parts not pressed on by the body-weight), on the neck, and the posterior aspects of the extremities of cadavers lying on their backs; and is to be

explained by the fact that after death the blood sinks to the most dependent parts of the body, and fills not only the veins, but finally the capillaries. This phenomenon is known as **post-mortem hypostasis,** and the areas of discoloration as **" death-spots "** or **livores.** They appear in a few hours after death, and are the more pronounced the greater the amount of blood contained in the skin and subcutaneous tissues at the time of death.

In the internal organs post-mortem hypostasis is particularly noticeable in the pia mater, the dependent veins being usually more markedly distended with blood than those situated higher. In the lungs the settling of the blood causes engorgement not only of the veins, but also of the capillaries.

If the circulation during life is imperfect, and tnere results general passive congestion, the blood may collect in the dependent portions of the body, partly because it is not driven out of them, and partly because it sinks into these parts from those situated on a higher level. This phenomenon is also known as **hypostasis,** and occurs particularly in the lungs (*hypostatic congestion*).

For the observation of the circulation and its disturbances during life the tongue or the web of the curarized frog spread on a glass plate may be used (*Cohnheim, Virch. Arch.,* Bd. 40), by drawing it over a cork ring, which is cemented to a glass plate, and fastening it to the sides of the ring with pins. The pulsating arterial current and the continuous venous stream possess a clear zone of bloodplasma, in both the normal and the quickened circulation. If, through ligation of the efferent veins, passive congestion is produced and the current slowed, the plasma-zone in the veins is lost, and both veins and capillaries become distended with red cells. After a time the tissue swells as the result of infiltration with transuded fluid.

According to the investigations of *von Landeerer* (" Die Gewebspannung," Leipzig, 1884), the wall of a capillary vessel supports only from one-third to one half of the blood-pressure. The remaining portion is borne by the tissues, which afford an elastic resistance, and thereby maintain the tension which is necessary to keep the blood in motion. In both active and passive hyperæmia tissue-pressure and tissue-tension are increased; in anæmia they are diminished.

§ 37. **Local anæmia** or **ischæmia** is the result of diminution in the afflux of blood. If the total mass of the blood is normal, the cause of the anæmia is purely local; if there is general poverty of blood, the local anæmia, in part at least, is secondary.

Pathological diminution in the blood-supply to an organ is at times merely the result of an *abnormal increase of the arterial resistance,* due to contraction of the circular muscular coat. In other cases *pathological obstructions* — such as compression of the arteries, narrowing of the lumen through changes in the vessel-walls, deposits on the inner surfaces of the arteries, occlusion by emboli (see Fig. 1, p. 47), etc. — act as hindrances to the blood-stream.

The immediate result of the *narrowing of an artery* is slowing of the blood-stream beyond the point of constriction. *Complete occlusion* of an artery brings the circulation beyond the obstruction to an immediate standstill. If back of the point of constriction or occlusion the artery is provided with communicating branches — the so-called *arterial collaterals* — the disturbance of the circulation may be compensated by increased afflux of blood through the collateral arteries; compensation is the more complete the larger and more distensible are the collaterals. If the narrowed or occluded artery possesses no collateral branches — if it is a so-

called *terminal artery*—the slowing or cessation of the circulation beyond the point of obstruction or occlusion cannot immediately be compensated for, and the affected area becomes partly or completely emptied of blood through contraction of the arteries and pressure of the tissues on the capillaries and veins.

When the current and the pressure beyond a *constricted point* sink to a certain minimum, the driving force gradually becomes unable to propel the mass of blood. The red corpuscles stagnate in the veins and capillaries, so that the *area supplied by the artery in question becomes again filled with blood,* which, however, is not in circulation, but at rest. *The same thing occurs when, after complete occlusion of a terminal artery,* the blood slowly and under low pressure enters the vessels of the affected area from small arteries incapable of adequate enlargement, or through anastomosing capillaries. Finally, accumulation of blood in the anæmic area may occur by reflux from the veins. This takes place when the intravascular pressure in the part has sunk to nothing in the arteries and capillaries, while in the veins a positive pressure exists. Passive congestion in the veins favors such reflux.

A further cause of anæmia of one organ may be found in abnormal congestion of other organs, since in that case the total quantity of blood is not sufficient adequately to supply the remaining organs. Such an anæmia is designated *collateral anæmia.*

All *anæmic tissues* are characterized by *paleness.*

The **significance of ischæmia** lies especially in the fact that, persistence of imperfect blood-supply brings about *tissue-degenerations* (compare § 1). Total arrest of the blood-supply leads in a short time to *death* of the tissue involved. If the blood comes to flow anew into the degenerating and dying tissues corresponding to the distribution of an obstructed vessel and there stagnates, extravasation may take place, leading to the formation of a *hæmorrhagic infarct* (compare § 44).

The rapidity and completeness of the *development of collateral circulation* after the occlusion of an artery depend on the size, number and distensibility of those vessels which are in communication with the anæmic area. If these are numerous and distensible, the anæmic area is soon supplied with an approximately normal volume of blood. If this is not the case the disturbance of the circulation is more slowly compensated; and the stasis and increased pressure are found to extend farther back from the point of obstruction toward the heart, so that collateral hyperæmia occurs in vessels situated farther back toward the heart. In the further course of re-establishing the circulation the increase of volume and velocity remains confined to such vessels as communicate with the area of the obstructed artery, that is, confined to the capillary and arterial anastomoses, where the increase in volume and velocity becomes permanent. This leads to lasting dilatation of the vessels concerned, and at the same time to an increase in the vessel-walls, not only in thickness, but also in length, as is evident from their tortuosity. According to *Nothnagel,* increase in thickness of the walls of the anastomosing arteries may be demonstrated in rabbits about six days after the ligation of an artery; after the ligation of large vessels, the small arteries which carry on the collateral circulation become in the course of a few weeks capacious and thick-walled.

III. Coagulation, Thrombosis, and Stasis.

§ 38. After *death* the **blood** in the heart and great vessels sooner or later **coagulates** with the formation of so-called **post-mortem clots.** If the clotting occurs at a time when the red blood-cells are evenly distributed, the whole mass of blood becomes coagulated, forming soft, dark-

red coagula which are known as **cruor**. If before clotting there occurs, through sinking of the red cells, separation of the blood into two layers— a substratum rich in red corpuscles, and an upper layer consisting of plasma—then, if the latter coagulate, there will be formed gelatinous,
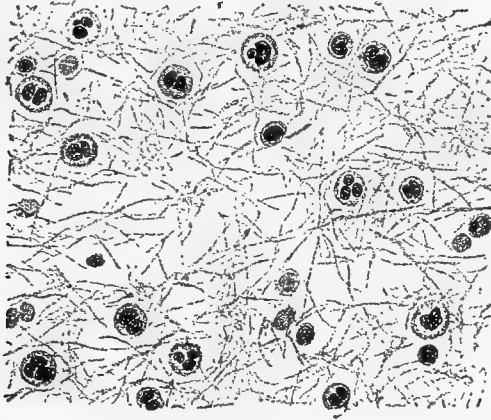
Fig. 8.—A lardaceous clot from the cadaver. (Formalin, hæmatoxylin, and eosin.) × 500.

light-yellow, elastic lumps and stringy masses having a smooth surface and **not adherent** to the vessel-wall, that are known as *lardaceous* or *" chicken-fat "* *clots.* These contain fibrin threads (Fig. 8) and scattered red and white blood-cells. Through the inclusion of red cells
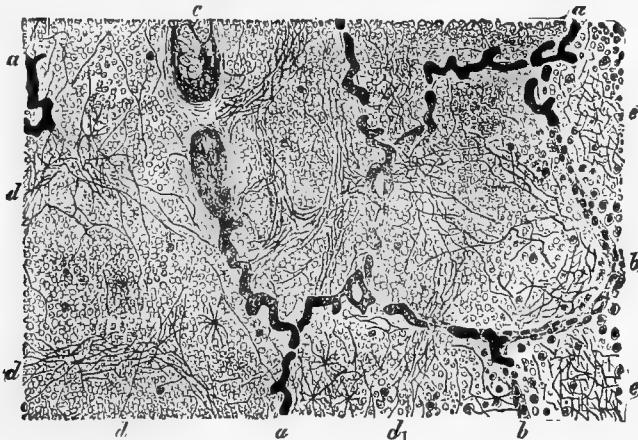
Fig. 9.—Coagulated blood in a fresh hæmorrhagic infarct of the lung. (Müller's fluid; hæmatoxylin and eosin.) *a,* Alveolar septa without nuclei, containing capillaries filled with dark bluish-violet, homogeneous thrombus-masses; *b,* septa containing nuclei; *c,* vein filled with red thrombus; *d, d₁,* alveoli filled with firm blood clots; *e,* alveoli filled with serous fluid, fibrin, and leucocytes. × 90.

in these formations, they may present in places a red or reddish-black color; if large numbers of leucocytes are present, they have a whitish color.

When blood is drawn from an artery or vein into a foreign receptacle, *coagulation* will occur in a short time, as the result of adhesion to the

sides of the receptacle. The blood becomes changed into a soft coherent mass. When freshly drawn blood is beaten with a solid body, the surface of the latter becomes covered in a short time with *fibrin. If in the body large quantities of blood pass into the tissues*—for example, into the pericardium or lungs—*coagulation* may likewise occur, and the extravasated blood acquires a firm consistence (Fig. 9).

Under certain conditions there may be formed *in the heart or blood-vessels during life, firm deposits,* which are similar to cruor or to the fibrin formed by whipping the blood. These formations are known as **thrombi,** and the process which leads to their formation is **thrombosis.** According to their color thrombi may be distinguished as *red,* or *white* (yellow or grayish-white), and *mixed.*

The pathogenesis of thrombosis centers in the chemistry of the coagulation of the blood. The substances necessary for coagulation are fibrinogen, fibrin ferment (thrombin) and calcium salts. Fibrinogen and calcium salts are normally present in the blood. Thrombin, on the contrary, is not present as such; otherwise coagulation would occur. It is supposed that it first appears in an inactive form—prothrombin. Morowitz and Fuld independently put forward an explanation to account for the activation of prothrombin, namely, that thrombokinase (the zymoplastic substance of Schmidt) in the presence of calcium salts transforms prothrombin into thrombin, as a result of which fibrinogen is coagulated.

FIG. 10.—Bundles and star-shaped clusters of fibrin threads within a blood-vessel. (Fibrin stain.) Preparation taken from an inflamed tracheal mucous membrane. × 500.

As to the origin of prothrombin and thrombokinase there is some uncertainty; prothrombin, however, is probably provided by the blood platelets and is either secreted by them or results from their disintegration. Thrombokinase, on the other hand, is derived from the blood platelets, the leucocytes, the vessel walls or from the tissues generally, the testis being a convenient source from which to obtain it for experimental purposes (Mellanby). The problem of thrombokinase is further complicated by the presence of coagulins in the vessel walls and tissues, extracts of which, as has long been known, produce coagulation of fibrinogen (Welch).

The immediate cause of ante-mortem intravascular coagulation is to be sought in increase in the fibrinogenic substance of the blood, together with diminution in the ability of the walls of the vascular apparatus to inhibit coagulation. Coagulation may be brought about by disturbances of the circulation, particularly retardation of the current and the formation of eddies which drive the blood plates against the vessel wall, and by changes in the vessel walls themselves.

The formed elements which may enter into the composition of thrombi are *blood platelets, fibrin, leucocytes* and *red corpuscles*. The diversity in appearance and structure of thrombi is dependent on variations in the number, proportion and arrangement of their constituents. Histologically, the intravascular clot is characterized by the formation of minute rods and threads which lie between the cellular elements as a delicate supporting meshwork or as stellate or fasicular groups arranged around centers. These rods and fibres are collectively known as fibrin and the centers around which the groupings occur are composed practically exclusively of blood platelets. The granular material found in thrombi, to which the older observers attached relatively little importance and which they interpreted as collections of finely divided fibrin or as detritus derived from white corpuscles, is now known to be an essential factor in the process of thrombosis and consists of blood platelets.
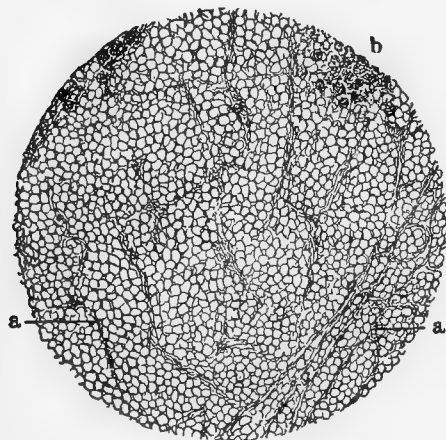
Fig. 11.—Section through a red thrombus formed in one of the veins of the thigh-muscles, after occlusion of the femoral vein. (Müller's fluid; hæmatoxylin.) *a*, Fibrin-threads; *b*, leucocytes and granular masses. × 250.

Bizzozero, in 1882, described a new element of the blood in the form of small homogeneous s t r u c t u r e s which he designated *blood plates*. He regarded them as identical with the haematoblasts previously described by Hayem. As a result of experimental investigations, Bizzozero concluded that these bodies played an important rôle in the coagulation of the blood. This view has been amply substantiated and is now universally accepted. At one time the blood platelets were regarded as disintegration products of the red cells. This view has been abandoned. Cole, for example, has produced a specific agglutinating serum for blood platelets and his experiments militate against a genetic relationship between platelets and red blood corpuscles. According to Wright, the platelets are fragments of the cytoplasm of the bone marrow giant cells and occur only in those vertebrates in whose marrow giant cells are found. The number of platelets increases or diminishes in proportion to the number of giant cells in the marrow. Platelets are a constituent of normal blood, but occur in great abundance only in pathological conditions. Following Eberth and Schimmelbusch, many observers explain the beginning of thrombosis by the accumulation of pre-existing platelets round a foreign body or on the damaged inner wall of the heart or vessels associated with slowing or irregularities in the blood current. Contact with the altered surface sets up immediate viscus metamorphosis of the platelets, as a result of which they adhere to one another or to the foreign body or vascular wall. For example, if, in a vessel whose circulation is

retarded, the intima is injured by compression or crushing or by chemical irritants, blood platelets may be seen adhering to the injured portion and in a short time the spot is covered. Variable numbers of leucocytes now become imbedded in the mass together with red cells which drop out of circulation and are entangled in the thrombus.

There are five outstanding varieties of thrombi: (a) *red*, (b) *white, mixed* or *laminated*, (c) *agglutinative* or *hyaline*, (d) *leucocytic*, (e) *fibrinous.*

(a) The **red thrombus** is formed in conditions attended by marked slowing of the circulation and is composed of red and white cells in the same relative proportions as they exist in normal blood, together with a network of fibrin (Fig. 11). In fresh clots in small vessels, it not
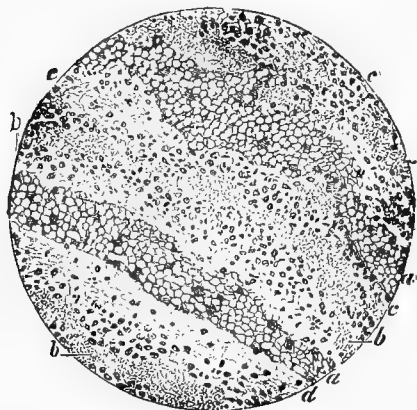
FIG. 12.—Section from a mixed thrombus rich in cells. (Müller's fluid, hæmatoxylin.) *a*, Red blood-cells; *b*, granular masses; *c*, reticular fibrin containing many leucocytes; *d*, threads of fibrin in parallel arrangement. × 200.

FIG. 13.—Section from a white thrombus containing but few cells. (Müller's fluid; hæmatoxylin.) *a*, Granular masses; *b*, fibrogranular fibrin forming a net-like reticulum; *c*, fibrin-threads in parallel arrangement. × 200.

infrequently is possible to demonstrate the presence of bundles and star-shaped clusters of fibrin, which radiate from centers composed of blood platelets. In such cases, however, it is not always possible to determine to what extent the coagulation is intra-vital or to what extent it is post-mortem. Such coagulation, however, is most frequently observed in inflammed tissues, and the conclusion seems warranted that in these circumstances it is a vital phenomenon.

(b) **White, mixed** and **laminated thrombi** arise from the circulating blood in diseases of the vascular apparatus which are attended by general or local slowing or by irregularity of the blood stream, and are yellowish or of various shades of red or of alternating layers of red and white. Microscopic examination shows them to consist of masses of platelets and thread-like collections of fibrin together with variable proportions of leucocytes, red cells and blood platelets. In mixed thrombi, fibrin and red blood cells are combined, often in alternate strata, and among these elements are greater or less numbers of leucocytes and blood platelets.

(c) **Agglutinative or hyaline thrombi**: Agglutinative thrombi occur in the smaller vessels—capillaries, arterioles and venules—and are characterized histologically by the appearance of closely packed and poorly defined red blood corpuscles which later become fused and transformed into a translucent hyaline substance. This variety of thrombosis has been observed in a number of conditions, among them, pneumonia, in the intestine in typhoid fever, and the stomach in carbolic acid poisoning. They are particularly frequently encountered, however, in the smaller branches of the hepatic veins in eclampsia and are associated with hæmorrhagic and necrotic foci in the parenchyma (hæmorrhagic hepatitis). Agglutinative thrombi may be produced experimentally by the injection of various micro-organisms, by ricin, ergot, freezing and hæmagglutinative sera.
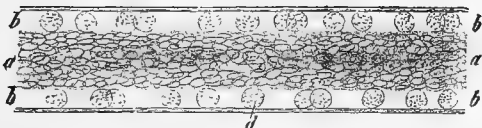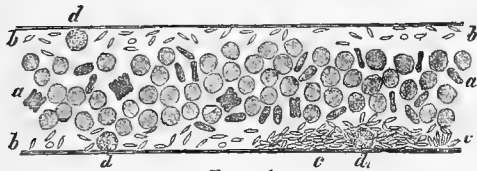
Fig. 14.

Fig. 15.

Fig. 16.

Fig. 14.—Rapidly flowing blood-stream. a, Axial stream; b, marginal zone with isolated leucocytes, d. (After Eberth and Schimmelbusch.)

Fig. 15.—Moderately slow blood-stream. a, Axial stream; b, peripheral zone with numerous leucocytes, d. (After Eberth and Schimmelbusch.)

Fig. 16.—Markedly slow current. a, Axial stream; b, peripheral stream with blood-plates; c, collection of blood-plates; d, d₁, leucocytes. (After Eberth and Schimmelbusch.)

(d) **Leucocytic thrombi:** In certain inflammatory processes, intravascular plugs occur which are made up wholly or predominantly of polynuclear leucocytes (Welch). Small vessels are sometimes plugged by lymphocytes in chronic lymphatic leukemia, in the walls of the appendix in conditions attended by excessive hyperplasia of the lymphoid elements normally resident in the submucosa, etc.

(e) In certain inflammatory lesions, notably croupous pneumonia, vessels of small size are sometimes encountered in which the lumen is more or less completely filled with fibrillated or whorl-like clumps of *fibrin*. An occasional leucocyte or small collections of platelets may sometimes be observed. This form of thrombosis is of negligible importance.

The **formation of thrombi** may be studied under the microscope, both in cold-blooded and warm-blooded animals; and observations made in this manner, especially by *Bizzozero, Eberth, Schimmelbusch,* and *Löwit,* have led to important results.

When the blood flows with normal velocity through a vessel, there may be seen under the microscope a broad, homogeneous red stream in the axis of the vessel (Fig. 14, *a*), while at the sides there lies a clear plasma-zone (*b*) free from red cells. This may be observed in the arteries and veins, but best in the veins, while in the capillaries, which are just large enough to permit the passage of the red cells, this difference between the axial stream and plasma-zone is not apparent.

In the axial stream the different constituents of the blood are not recognizable; in the plasma-zone there appear, from time to time, white corpuscles (Fig. 14 *d*), which roll slowly along the vessel-wall.

If the blood-stream becomes retarded to the degree that the red cells of the axial stream are indistinctly recognizable (Fig. 15, *a*), the white corpuscles which roll slowly in the plasma-zone, at times adhering to the vessel-wall, become constantly increased (Fig. 15, *d*), so that they finally lie in great numbers in this zone.

If the current is still further retarded so that the red cells become plainly recognizable (Fig. 16, *a*), there appear in the peripheral plasma-zone, in addition to the colorless corpuscles (*d*), blood-plates (*b*), which increase in number with the retardation of the current, while the leucocytes again become diminished. When arrest of the blood-current occurs, there follows a distinct separation of the corpuscular elements in the lumen of the vessel.

If, in the vessel in which the circulation is retarded, the intima is injured at a certain point by compression or crushing, or by means of chemical agents, as corrosive sublimate, nitrate of silver, or sodium chloride, and if the lesion of the wall does not lead to complete stoppage of the circulation, *blood-plates* may be seen *adhering to the injured portion;* and in a short time the injured spot is covered with many layers (Fig. 16, *c*). Often *leucocytes* (d_1) become embedded in this mass, and their number is the greater the more numerous they are in the plasma-zone. Under certain conditions they may partly cover the blood-plates. In case of great irregularity of the circulation or more severe changes in the vessel-wall, *red cells* may *become adherent* to the vessel-wall or to the colorless deposit already formed. Not infrequently portions of the thrombus-mass are torn loose and a new deposit of blood-plates occurs. The vessel may finally be closed as the result of continued deposit of the blood-elements.

When at any point blood-plates in large numbers have become adherent to the vessel-wall, they become after a time adherent to one another and finally fused into a compact mass. Eberth designates the sticking together of the blood-plates *conglutination,* their fusion as *viscous metamorphosis.*

If we compare the observations made on warm-blooded animals by *Bizzozero, Eberth,* and *Schimmelbusch,* and more recently by *Löwit* and *Gutschy,* with the histological findings in thrombi occurring in the human subject, we are warranted in the conclusion that the formation of thrombi in the circulating blood of man occurs in the same way as that observed in the lower animals. Thrombosis is, therefore, directly dependent on two causes: **disturbances of the circulation**, particularly *retardation of the current and the formation of eddies which drive the blood-plates against the vessel-wall;* and **local changes in the vessel-walls**. It is also probable that thrombosis is favored by **pathological changes in the blood**. From the variety of conditions under which thrombosis in man occurs, we must assume that at one time one cause, at another time another, plays the chief part in the formation of the thrombus, or that all three may take an equal part.

According to *Arthus* and *Pagès,* the blood flowing from the veins becomes incapable of coagulating spontaneously if sodium oxalate, sodium fluoride, or soaps are added to it in such quantities that the mixture contains 0.07–0.1 per cent of the oxalate, or about 0.2 per cent of the fluoride, or 0.5 per cent of soap. These act by precipitating the calcium salts. If to blood, kept fluid by treatment with oxalic acid, one-tenth of its volume of a one-per-cent solution of calcium chloride is added, coagulation occurs in six to eight minutes, and the calcium salts pass into the combination of the fibrin-molecule. The fibrin-ferment can act on the fibrinogen only in the presence of calcium salts. Under the influence of the fibrin-ferment, and the presence of calcium salts, the fibrinogen undergoes a chemical change which results in the formation of a calcium-compound, fibrin. *Hammarsten,* who holds that the presence of calcium is not necessary for the change of fibrinogen into fibrin, attempts to explain the observation of *Arthus* and *Pagès,* on the assumption that the calcium salts are necessary factors for the conversion of prothrombin into thrombin.

If blood be allowed to flow beneath a layer of oil, into a vessel coated with a film of vaseline, it will not coagulate (*Freund*); and from this it may be assumed that the cause of coagulation is to be found in the adhesion of the blood to a foreign body.

A. Schmidt, in his work on the blood, published in 1892, in which he collects the results of many years of study on the coagulation of the blood, regards the fibrin-ferment or *thrombin* as a cell-derivative, which arises from an inactive antecedent substance, *prothrombin,* under the influence of certain *zymoplastic substances* which are also cell-derivatives. He likewise regards the *fibrinogenic substance,* or *metaglobulin,* as a product of disintegration of cellular protoplasm.

§ 39. According to the cause of the injury to the vessel-wall there may be distinguished: *traumatic, infectious,* and *thermic thrombi,* as well as those *produced by degenerative changes in the wall, foreign bodies,* and *tumor proliferation.* Thrombi occurring in individuals with poor circulation are designated *marasmic* or *cachectic.*

Thrombi also may be classed according to their relation to the vessel-lumen. Thus thrombi attached to the wall of the heart (Fig. 17, *a*) or blood-vessel are known as **parietal thrombi,** those situated on the valves of the heart or veins (Fig. 18, *d*) are termed **valvular thrombi.** In both cases the thrombi may consist only of delicate, membranous, translucent or hyaline deposits; but are often thick and firm and project into the lumen of the heart or vessels. Their surface often shows ribbed elevations which are paler than the other portions. A thrombus completely closing the lumen of the vessel is called an **obturating thrombus** (Fig. 18, *a, b*). The coagula first formed are designated **primary** or **autoch-**
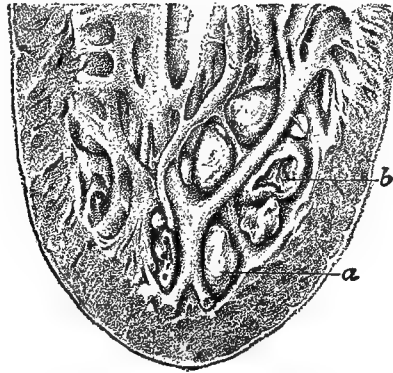
FIG. 17.—Polypoid heart thrombi firmly attached between the trabeculæ of the left ventricle. *a,* Thrombus with smooth surface; b, thrombus with open cavity of degeneration. (Natural size.)

thonous, those subsequently deposited on these as **induced thrombi.** Through growth by accretion a parietal thrombus may become changed to an obturating one. In this way it not infrequently happens that on an originally white or mixed thrombus a red one (Fig. 18, *c*) is formed; the thrombosis at the beginning occurring in circulating blood, while later, after closing of the vessel, the blood comes to a standstill and clots *en masse.* The reverse may occur—that is, on a thrombus originally red there may be deposited white or mixed coagula—when a red thrombus obturating a vessel becomes smaller by contraction, and thus opens up a channel for the passage of blood.

Thrombi may occur in any part of the vascular system. **In the heart** they are formed chiefly in the auricular appendages and in the intertrabecular spaces, or on any diseased spot (Fig. 17, *a*) in the heart-wall. They begin usually in the recesses between the trabeculæ, but through continual accretions form large coagula which project above the surface in the form of polypoid masses (Fig. 17). They are sometimes more or less spherical in shape, with a broad base; at other times club-shaped; their surface is ofted ribbed. In rare cases large spherical or knobby thrombi may become loosened; and, if they cannot pass the ostium, lie

free in the corresponding chamber of the heart.   Such **free globular thrombi** are sometimes seen in the auricles in stenosis and insufficiency of the auriculo-ventricular orifices.   After detachment they may increase in size through new deposits of fibrin.   Masses of coagula which are deposited on inflamed valves are known as **valvular polypi**.   Parietal and valvular polypi may reach such proportions as to fill a large part of the heart-chambers.

In the arterial trunks thrombi may occur in a variety of places, particularly behind constrictions and in dilatations.   Occasionally in cachectic individuals with a degenerate intima, parietal, white, or mixed thrombi, adherent to the surface, are formed in the aorta.

In the veins thrombi are occasionally formed in the pockets of the valves (Fig. 18, d), from which they may protrude and develop into obturating thrombi.   Often a thrombus may grow from a smaller vein (a), where it was primary, into the lumen of a larger vein (b).   Thus, a thrombus having its origin in a small vein of the lower extremity may grow into the inferior vena cava and even reach the heart.   Of especial importance, because of the resulting local disturbances, are the obturating thrombi of the femoral veins, the renal veins, the sinus of the dura mater, the venæ cavæ, and the portal veins.

Thrombosis in the small vessels is most frequently the result of disease of the surrounding tissues, particularly infectious, toxic, and necrotic processes.   The thrombi are, for the greater part, hyaline; in their composition the red blood-corpuscles

Fig. 18.—Thrombosis of femoral and saphenous veins. *a, b,* Obturating mixed and laminated thrombus; *c,* red thrombus showing peripheral attachment; *d,* thrombus protruding from a valve. (Reduced one-fourth.)

have the chief share, fusing into a homogeneous mass.   Nevertheless, it may be demonstrated occasionally, by means of proper technique (Weigert's staining method), that they also contain fibrin.   Thrombi of smaller vessels occur also after burns of the skin (Klebs, Welti, Silbermann) and often in cases of poisoning—for example, with corrosive sublimate (Kaufmann)—and are found especially in the smaller vessels of the lung.   They frequently occur in hæmorrhagic infarcts (Fig. 9, a). Thrombi originating in the capillaries may involve the efferent veins, partly for the reason that through obturation of numerous capillaries the blood flows more slowly into the veins, partly for the reason that disintegrating red cells and blood-plates pass into the veins in large numbers.

The **first deposits** in the formation of a parietal thrombus consist of delicate, translucent, or whitish layers. The **fully formed thrombus** is a rather firm, dry mass, adherent to the inner surface of the vessel or heart, and in color and structure varying according to the conditions mentioned above. Thrombi, originally soft and moist, undergo in time a process of **contraction,** and become firmer and more dry. By means of contraction vessels closed by obturating thrombi may become partially opened for the passage of blood.

In the event of marked contraction, the fibrin, blood-plates, and red cells become changed into a firm mass, which may remain in this condition for a long time, and finally undergo **calcification.** This may occur in both valvular heart-thrombi and thrombi located in the vessels. The chalky concretions formed in the veins are known as **phleboliths;** those occurring in the arteries as **arterioliths.**

Contraction and calcification are relatively favorable sequelæ of thrombosis. Much less favorable are the more frequent processes of degeneration occurring in thrombi, which are known as simple and as puriform softening. In **simple softening** the central portion of the thrombus becomes changed into a grayish-red, or gray, or grayish-white grumous mass, consisting of disintegrated and shrunken red corpuscles, pigment-granules, and colorless, granular débris. If the softening extends to the superficial layers, and if there is sufficient strength of blood-current in the neighborhood of the thrombus, the products of disintegration may be swept into the circulation. If larger pieces become loosened and transported by the blood-stream emboli are produced (see Fig. 1, page 47).

FIG. 19. — Remains of a thrombus of the right femoral vein occurring three years before death. *a,* Obliterated portion of the vein (the right common iliac artery was also obliterated); *b, c, d,* connective-tissue cords in the lumina of the vein and its branches; *e,* fresh thrombus. (Natural size.)

In **puriform softening** the thrombus breaks down into a yellow, or grayish-yellow, or reddish-yellow, grumous, creamy, and at times foul-smelling mass, consisting of pus-corpuscles and a large amount of finely-granular substance, composed of fatty and albuminous detritus and micrococci or other bacteria.

The process of softening of a thrombus, associated with purulent infiltration of the vessel-wall, is designated purulent **thrombophlebitis** or **thrombo-arteritis** accordingly as it involves a vein or an artery. The inflammation of the vessel-wall may take its start either in the softening thrombus or in the tissues adjacent to the vessel. In the latter case softening of the thrombus is coincident with the inflammation of the vessel-wall or follows it. These processes occur most frequently in the neighborhood of purulent foci.

The most favorable sequel of thrombosis is **organization of the thrombus**—that is, **substitution of the thrombus by vascularized**

connective tissue derived from the proliferating cells of the vessel-wall. The thrombus itself takes no part in the organization; it is a dead mass which excites proliferation of the surrounding tissues (Fig. 20, *b, c, d*).
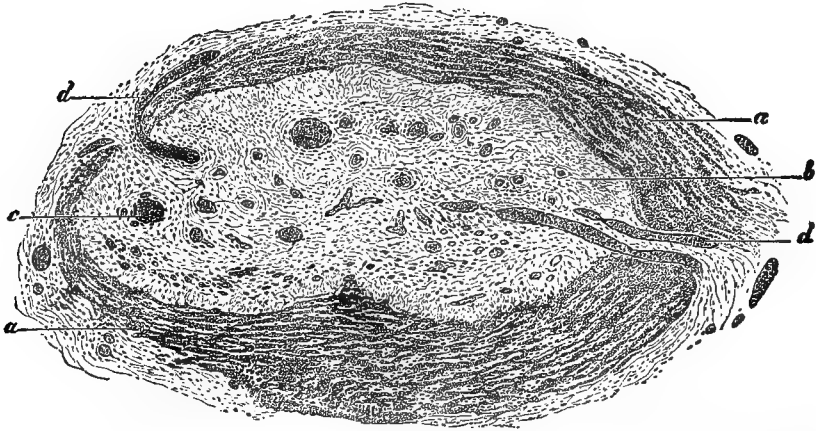
Fig. 20.—Obliteration of a pulmonary artery by connective tissue after embolic plugging of its lumen. (Müller's fluid, hæmatoxylin, and eosin.) *a*, Artery wall; *b*, connective tissue filling the vessel-lumen; *c, d*, newly formed blood-vessels. × 45.

The cicatricial tissue formed in the place of the thrombus contracts in the course of time. Cicatrices formed after ligation may thus become very small. Such a cicatrix in the continuity of a vessel may appear simply as a thickening of the vessel-wall, or there remain only threads and trabeculæ (Fig. 19, *b, c, d*), which cross the lumen of the thrombosed vessel, so that the blood-stream can once more pass the affected spot. Not infrequently the connective-tissue strands crossing the vessel cause marked narrowing of the lumen; or the vessel may become obliterated (Fig. 19, *a*), and converted for a greater or less distance into a fibrous cord.

Pieces broken from a thrombus and carried into an artery and lodged —that is, **emboli**—induce new deposits of fibrin on their surface. Later they undergo the same changes as thrombi, and may soften, contract (Fig. 21, *a*), or become calcified. If the emboli are non-infective they are apt to be replaced by vascular connective tissue (Fig. 20, *b, c*).

Fig. 21.—Remains of embolic plugs in a branch of the pulmonary artery. *a*, Contracted embolus traversed by connective-tissue threads; *b*, cords of connective-tissue crossing the orifices of branch vessels. (Natural size.)

In many cases the new-formation of connective tissue leads to obliteration of the artery (Fig. 20). In other cases in the place of the embolus there is developed only a ridge of connective tissue or a nodular

or flat thickening of the intima. In still other cases the lumen of the vessel is traversed by strands of connective tissue (Fig. 21, *b*), which either run separately or form a fine- or coarse-meshed network.
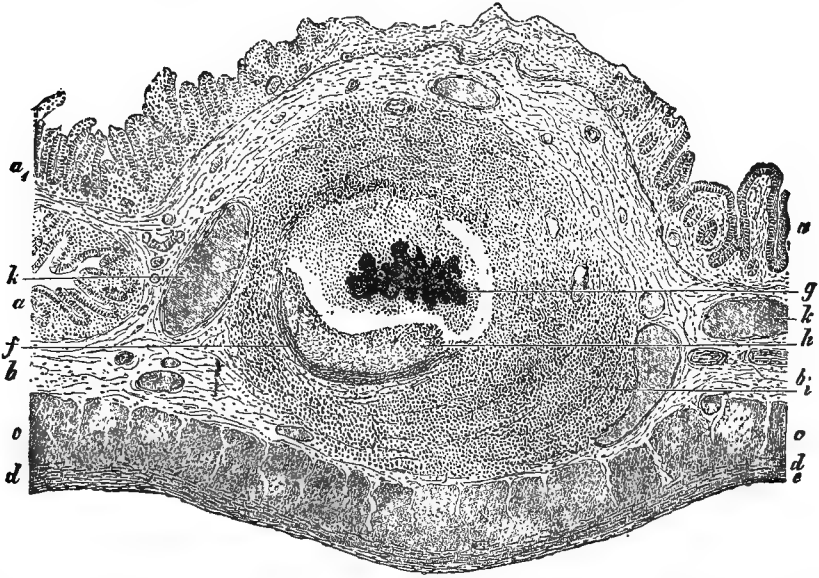
FIG. 22.—Embolism of an intestinal artery, with suppurative arteritis, embolic aneurism, and periarterial, metastatic abscess. (Alcohol, fuchsin.) *a, b, c, d, e,* Layers of the intestinal wall; *f,* artery wall; *g,* embolus, surrounded by pus-corpuscles, lying in the dilated artery which is partly destroyed by suppuration; *h,* parietal thrombus; *i,* periarterial purulent infiltration of the submucosa; *k,* veins gorged with blood. × 27.

If pyogenic organisms are present, as is the case when the emboli arise from a thrombus lying in a suppurating focus, a purulent process is produced (Fig. 22, *i*) at the site of lodgment (Fig. 22, *g*).

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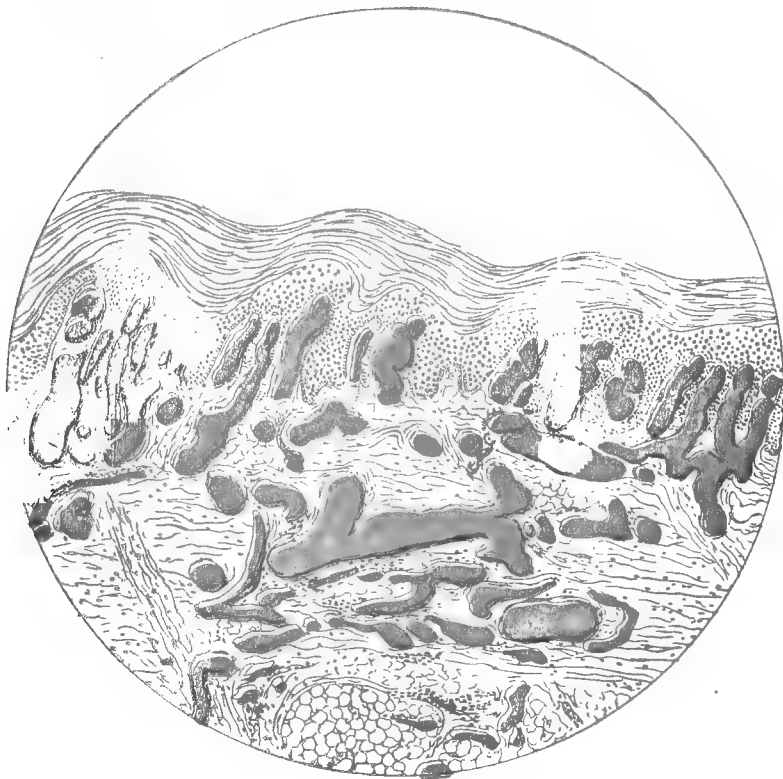
FIG. 23.—Congestive stasis in the vessels of the corium and papillæ of the plantar surfaces of the toes from a man dying of valvular disease, heart failure, and arteriosclerosis. (Müller's fluid, alum carmine.) Toes presented a deep violet color, and beginning gangrene. × 20.

§ 40. **Stasis** or **stagnation** is characterized by retardation of the circulation without coagulation of the blood. The red blood-cells are so closely pressed together that the small vessels are filled or distended, and the outlines of the individual cells cannot be distinguished (Fig. 23), The condition is one of marked *passive congestion*. When the blood entering a certain area finds its avenues of escape impeded, the circulation in the small veins and capillaries, and even in the smallest afferent arterial branches, comes to a state of almost complete arrest. Since from the arteries there come with every pulse-wave fresh masses of blood to the congested area, the capillaries and veins become distended

and the pressure within these rises to the height of that at the point of divergence of the nearest permeable artery. In this way the red blood-cells become so closely packed that their contours are no longer distinguishable, and the contents of the vessel form a homogeneous, scarlet-red column (Fig. 23). The red blood-cells, however, are not fused; as soon as the impediment to the outflow is removed and the circulation is restored, the corpuscles become once more separated from one another.

Stasis may be caused by many influences which affect the vessel-wall and the blood itself. Thus, *heat and cold, acids and alkalies, concentrated solutions of sugar and salt, chloroform, alcohol, etc.,* cause stasis. These act by abstracting water from the blood, and by producing changes in the composition of the corpuscles, and vessel-walls; as a result, the red cells become less mobile and the vessel-walls offer increased frictional resistance to the blood-stream, and at the same time permit the fluid portions of the blood to pass through more readily.

IV. Œdema.

§ 41. The fluid which permeates the tissues is essentially a transudate from the blood, though under certain conditions fluids contained in cells and fibres may also pass into the intervening spaces. The passage of fluid from the vessels is in part a process of filtration and in part a
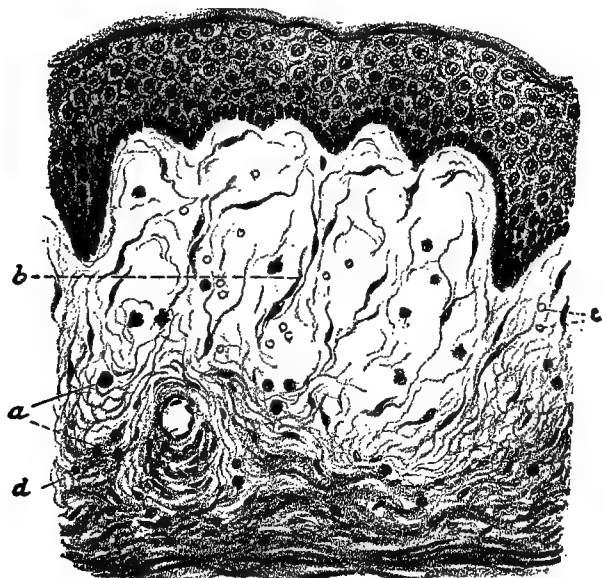
FIG. 24.—Stasis-œdema of the papillary bodies of the skin of the leg from a case of mitral stenosis. (K. Ziegler, l. c.). *a*, Lymphocytes; *b*, connective tissue fibrillæ with cells; *c*, red blood-cells; *d*, blood-vessel. × 300.

secretion, accomplished by means of a specific function of the capillary walls. The fluid secreted by the capillaries mingles with the products of metabolism in the tissues, and is taken up by the lymph-vessels, and through the thoracic duct is returned to the blood.

Increase in the transudation of the fluids of the blood causes more marked saturation of the tissues, which may be compensated for by absorption through the lymph-vessels. This compensation has, however, its limits; with increased transudation from the blood-vessels there is produced more or less permanent over-saturation of the tissues.

The condition produced by collection of fluids in the tissues is known as **dropsy, œdema,** or **hydrops.** According to its extent there may be distinguished *general* and *localized hydrops.* Œdema extending over the superficial portions of the body is known as **anasarca.**

The transudate from the blood which constitutes œdema or hydrops is poorer in albumin than the plasma. The fluid collects at first in the tissue-spaces, pushing apart the tissue-elements (Fig. 24, *b*), but may soak into the tissue-elements themselves and cause *swelling* of cells and fibres, and, under certain conditions, the formation of so-called *vacuoles* (Fig. 25), due to the collection of droplets in the cells.
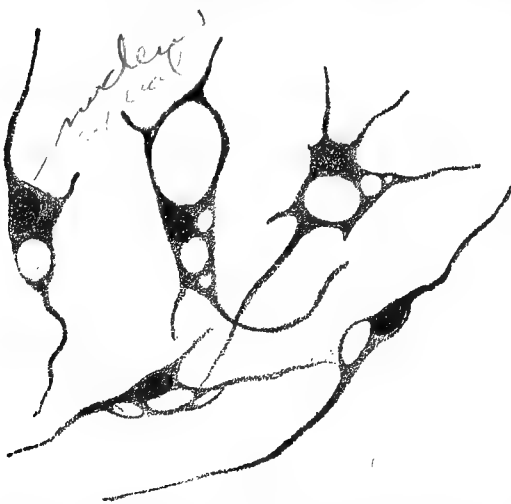
FIG. 25.—Hydropic connective-tissue cells from the subcutaneous tissue of a case of chronic œdema due to stasis. (K. Ziegler, l. c.) × 400.

This may be frequently demonstrated in the epithelium of the body-surfaces and of glands, but at times becomes evident in other tissue elements—for example, in connective-tissue cells and muscle-fibres (Figs. 25, 26). Moreover, it often happens in œdematous tissues that cells become loosened from their basement-membrane, particularly in the lungs and serous membranes and are mixed with the fluid. In œdema of the skin, the epidermis (Fig. 27) may be separated and lifted from the papillary bodies, while the fibrillæ of the latter are pushed apart.

Tissues which are the seat of œdema are swollen. The degree of swelling depends on the structure of the affected tissue. The skin and subcutaneous tissue are able to take into their lymph-spaces large quantities of fluid, so that an extremity may become enormously swollen. In this condition it is pale, doughy in consistence, and pits on pressure. On incision an abundance of clear fluid escapes.

The lung behaves in a similar way. Owing to limited space it cannot become greatly distended, but it contains vast numbers of alveoli filled with air which, in the advent of œdema, is displaced by fluid, and this on pressure escapes from the cut surface, mingled with air-bubbles.

Œdema of the kidney, which may become marked, is caused by retention in the dilated tubules of the water secreted by the glomeruli. In the connective tissue between the tubules infiltration of fluid may also occur.

The amount of blood contained in œdematous tissues is variable, and their color varies accordingly.

Body-cavities which are the seat of dropsical effusion contain at one time a large, at another time only a small amount of clear, usually light-yellow, rarely colorless, alkaline fluid, which at times contains a few fibrin flakes (see the chapter on Inflammation). Organs are compressed by the effusion; cavities are dilated.
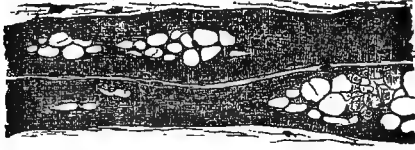
FIG. 26.— Longitudinal section of œdematous muscle-fibres from the calf muscles in a case of chronic œdema of the legs. (Flemming's solution, safranin.) × 45.

A collection of transuded fluid in the abdominal cavity is known as **ascites**.

The albumin-content of transudates is not the same in all the cavities and tissues, but differs in pronounced degree. According to Reuss, the albumin-content of transudations of the pleura is 22.5 *pro mille;* that of the pericardium, 18.3; of the peritoneum, 11.1; of the subcutaneous connective-tissue, 5.8; of the membranes of the brain and spinal cord, 1.4. These facts may be taken as proof of the different constitution of the vessel-walls in the various tissues of the body.

§ 42. According to their etiology we may distinguish **five varieties of œdema**: œdema due to *arterial congestion;* œdema *from stagnation of blood;* œdema *caused by hindrance to the outflow of the lymph;* œdema
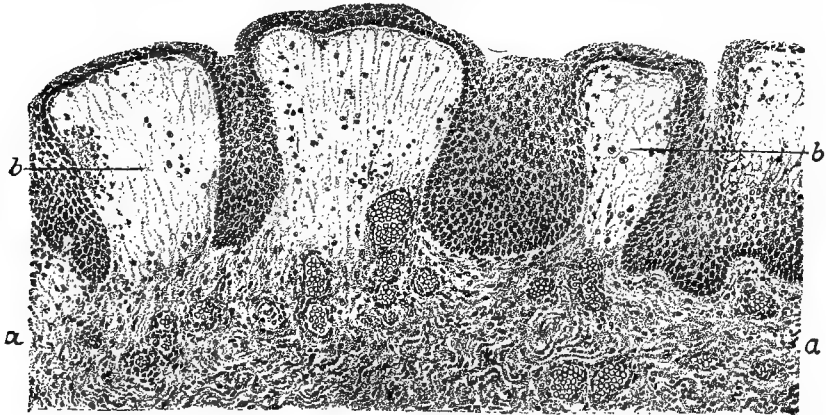
FIG. 27.—Inflammatory œdema of the papillary bodies, with elevation of the epidermis from the papillary bodies by an inflammatory exudate, from a case of phlegmon of the thigh. (K. Ziegler, l. c.) *a*, Corium; *b*, exudate consisting of fluid, fibrin and leucocytes. × 40.

caused by disturbance of the capillary secretion due to changes in the capillary walls; and *œdema ex vacuo.* The fourth is designated inflammatory, hydræmic or cachectic, or neuropathic œdema, according to the clinical features.

Œdema due to arterial congestion occurs acutely in localized areas, in the skin and subcutaneous tissue, larynx, bronchi (asthma), nose, periosteum, and muscles (angio-neurotic œdema). In individuals show-

ing the tendency in marked degree, bullæ may be formed in the skin. In angio-neurotic œdema toxic influences assume an important part. It not uncommonly happens, for example, that the ingestion of strawberries, oysters, etc., is succeeded by œdema of the eye-lids of such an extent as to produce closure; if the soft tissues of the larynx are involved symptoms of suffocation may arise and death may occur from occlusion of the glottis. Urticaria is a variety of angio-neurotic œdema. It is probable that thè changes in question are of the nature of anaphylactic phenomena.

Œdema due to stagnation of blood arises when, as a result of impediment to the outflow of blood, the pressure in the capillaries rises and the fluid of the blood seeks a lateral outlet, so that an increased amount escapes. The amount of escaped fluid is larger the greater the discrepancy between inflow and outflow; it is therefore increased through coincident increase of the inflow. The escaping fluid is always poor in albumin, but with increased pressure in the veins the albumin-content is increased (Senator).

The immediate result of increased transudation from the bloodvessels is increase in the lymph-flow, and this may be sufficient to carry off the fluid. If it does not suffice, the fluid collects in the tissue-spaces and œdema results. According to Landerer, this is favored by the fact that the elasticity of the tissues becomes diminished as the result of the long-continued increase of pressure to which they are subjected.

Obstruction to the outflow of lymph, as experiments have shown, is not ordinarily followed by œdema. The lymph-vessels possess such extensive anastomoses that obstruction to the outflow does not readily occur. Even when all the lymph-channels of an extremity are obstructed, if the amount of lymph formed is normal no œdema results, inasmuch as the blood-vessels are able to take up the lymph. Only *occlusion of the thoracic duct* is likely to lead to stagnation of lymph and the production of œdema, particularly ascites, but even in this case collateral channels may be opened in sufficient numbers to carry off the lymph.

Although lymphatic obstruction is not ordinarily sufficient in itself to produce œdema, it does increase œdema caused by concomitant transudation from the blood-vessels.

Pathological changes in the walls of the capillaries and veins of such nature as to cause increase in the vascular secretion, and thus to give rise to œdema, may occur as the result of *long-continued congestion* and imperfect renewal of blood. Such changes occur, however, more frequently as the result of prolonged *ischæmia, lack of oxygen, action of high or low temperatures,* the *development of tumors* (especially in the serous membranes), *infection,* and *intoxication.* It is also probable that *irritation or paralysis of the vasomotor nerves* may lead to increase of vascular secretion. Just what changes the vessels suffer under these conditions we are not able to state, but it may be assumed that alteration of the endothelial cells and of the cement-substance renders the vessels more permeable. The œdemas so produced may be classed according to their cause as **toxic, infectious, thermal, traumatic, ischæmic, neuropathic,** etc.; and such a classification has much to commend it. Hitherto the forms of œdema under consideration, with the exception of the neuropathic, have been arranged in two groups—namely, inflammatory and cachectic.

Inflammatory œdema is to be referred to alteration of the vessel-wall, and occurs as an independent affection, in the form of circumscribed or diffuse swelling or as hydropic effusions, and as a coincident phenomenon in the neighborhood of inflammatory processes. In the latter case it is designated *collateral œdema*. Inflammatory is distinguished from stagnation-œdema by the fact that the transuded fluid is *richer in albumin* and *in the number of white blood-corpuscles,* and in the fact that larger masses of coagula (Fig. 27, *b*) occur in it (see chapter on Inflammation). Its cause is to be sought in infectious and toxic, sometimes in thermal and traumatic influences, at other times in temporary ischæmia.

As to **hydræmic** or **cachectic œdema**, it was formerly believed that hydræmia—that is, diminution of the solid elements of the blood—as well as hydræmic plethora—that is, retention of water in the blood—could cause increased transudation from the vessels. It was supposed that the vessel-walls behaved as dead animal membranes, and allowed fluid poor in albumin to filter more easily than one rich in albumin. The vessel-wall is not, however, a lifeless membrane, but a living organ. Hydræmia experimentally produced does not, according to Cohnheim, give rise to œdema. Even when hydræmic plethora is produced by filling of the blood-vessels with watered blood, and is followed by increased transudation, leading to œdema, the œdema so produced occurs only when the proportion of water becomes very high, and does not develop in the same regions where the so-called hydræmic œdema in man appears. We must therefore assume that the œdema of cachectic individuals, as well as that occurring in individuals suffering from impairment of renal function, depends on *alteration of the vessel-wall,* caused either by the hydræmic character of the blood or by a poison or poisons in the blood. Probably other lesions through which the elasticity of the tissues is diminished are also concerned. *Hydræmia favors the occurrence of œdema,* but is not the sole cause and certainly does not determine its localization.

Cachectic œdema is allied to stagnation-œdema and to inflammatory œdema, in that at one time the circulatory disturbance is a prominent feature, at another time the vascular alteration.

Œdema ex vacuo occurs chiefly in the brain and spinal cord, and arises when a portion of the brain or cord is lost and not replaced by other tissue. In atrophy of the brain or cord the subarachnoid spaces become enlarged, occasionally the ventricles. The fluid has the same albumin content as the normal cerebrospinal fluid. Local defects become filled by dilatation of the nearest subarachnoid spaces or of the adjacent portions of the ventricles, or through collection of fluid at the site of the defect itself.

V. Hæmorrhage and the Formation of Infarcts.

§ 43. By **hæmorrhage** is understood the escape of all the constituents of the blood from the vessels (*extravasation*) into the tissues or on a free surface. It may be *arterial, venous,* or *capillary,* or from the *heart.* The blood which has escaped is termed an **extravasate.** For special forms of hæmorrhage a variety of terms is used. If the hæmorrhagic foci are small, and form more or less sharply outlined, punctate, red or

dark-red spots, they are called *petechiæ;* if larger and not sharply out-
lined, they are known as ecchymoses, or suggillations. If the tissue is
firmly infiltrated with escaped blood, but not torn or destroyed, the con-
dition is spoken of as a *hæmorrhagic infarct.* If the extravasated blood
forms a large mass, it is known as a *hæmatoma.*

The blood which escapes from the vessels into the tissues collects in
the tissue spaces (Fig. 28). Large hæmorrhages may completely conceal
the structure of the tissue (Fig. 29, *d*). Delicate tissues, as those of the
brain or spinal cord, may be destroyed by large hæmorrhages.

If the hæmorrhage occurs on the free surface of an organ, the blood
either escapes externally or is poured into a neighboring cavity.

Hæmorrhage from the nose is called *epistaxis;* vomiting of blood
hæmatemesis; bleeding from the lungs, *hæmoptysis;* from the uterus,
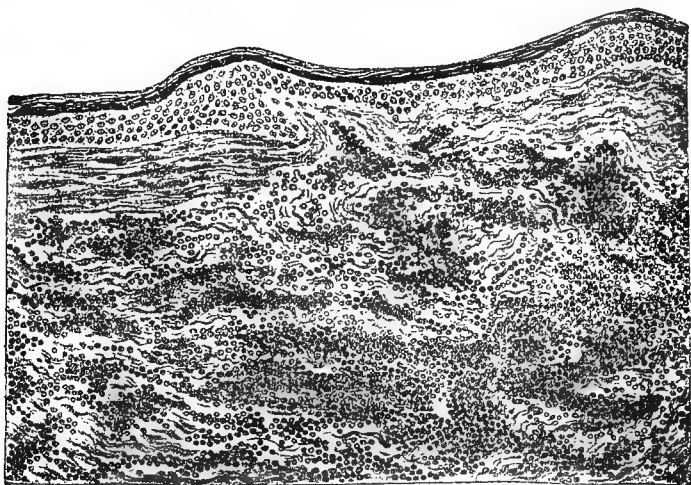
Fig. 28.—Hæmorrhage in the skin near the knee; from a man eighty-one years of age. (Formalin,
hæmatoxylin, and eosin.) × 80.

metrorrhagia and *menorrhagia* (during the menses) ; hæmorrhage from
the urinary organs, *hæmaturia;* from the sweat-glands, *hæmatidrosis.*

A collection of blood in the uterine cavity is designated *hæmatometra,*
in the pleural cavity *hæmothorax,* in the tunic of the testicle *hæmatocele,*
in the pericardium *hæmopericardium,* in the peritoneum *hemoperitoneum,*
etc.

Hæmorrhages of the skin not caused by trauma are termed *purpuric*
(Fig. 28). Collections of blood and fluid beneath the epidermis in place
of the dissolved deeper epithelial layers are known as *hæmorrhagic
blebs.*

Recent extravasations show the color of either arterial or venous
blood. Later the extravasate shows alterations characterized particularly
by color-changes. Suggillations of the skin become brown, then blue,
and green, and finally yellow. In time the extravasate is absorbed (see
Chapter V.), and during absorption tissue-proliferation often occurs.
Large collections of blood may become organized into connective tissue
or be encapsulated (see Chapter VII.).

Hæmorrhage may occur from **rupture of the heart** or **vessel-wall** —that is, **per rhexin** or **per diabrosin**. This is the only form of cardiac and arterial hæmorrhage. From the capillaries and veins hæmorrhage may also occur **per diapedesin**—that is, the red cells escape through the vessel-wall without the occurrence of a tear. Often such hæmorrhages are small and of slight extent; in other cases the process continues for a longer time, and infiltration of the tissues reaches a significant degree. Hæmorrhages by diapedesis are not always small, hæmorrhages by rhexis not always large. Rupture of a capillary or

FIG. 29.—Traumatic cerebral hæmorrhage. (Formalin, hæmatoxylin, and eosin.) *a,* Normal brain substances; *b,* blood-vessel; *c,* perivascular collection of blood; *d,* larger area of hæmorrhage with destruction of the brain substance. × 100.

small vein does not give rise to a large hæmorrhage; on the other hand, hæmorrhage through diapedesis can reach an important size.

The **causes of interruption of continuity of the heart and vessel-walls** are *traumatic injuries, increase of intravascular pressure,* and *diseased conditions of the heart and vessel-wall.* Increase of pressure in the capillaries and smallest veins can lead to rupture without the aid of vascular changes, particularly in marked passive congestion. The heart, normal arteries, and normal veins of large size cannot be ruptured through increase of pressure alone, but abnormally thin-walled or diseased areas in the heart, arteries, or veins may be so ruptured. Newly formed vessels are easily torn.

Diapedesis may be caused by *increase of pressure* in the capillaries and veins, as well as by *increased permeability of the vessel-wall.* If the outflow of the venous blood in a given area be obstructed, diapedesis of red cells from the capillaries and veins takes place as a result of increased pressure in the vessels. Diapedesis as a result of changes in the vessel-wall occurs particularly after mechanical, chemical, and thermal

injuries. Further, abnormal permeability of the vessel-walls is observed when for a long period the vessels have not been traversed by the blood-stream, and their nutrition has suffered in consequence.

When an individual shows a special tendency to hæmorrhage, the condition is designated **hæmorrhagic diathesis**. Two forms may be distinguished—congenital and acquired.

Congenital hæmorrhagic diathesis or **hæmophilia,** depends most probably on abnormal constitution of the vessel-walls. The composition of the blood may also be pathological, so that a hæmorrhage once started is not arrested, as usual, by coagulation of the blood.

Acquired hæmorrhagic diathesis occurs in those diseases known as scurvy, morbus maculosus Werlhofii, purpura simplex, purpura (peliosis) rhuematica, purpura hæmorrhagica, hæmophilia, and melæna neonatorum (gastric and intestinal hæmorrhages) ; in many infections—septicæmia, endocarditis, typhus fever, cholera, smallpox, plague, yellow fever; in intoxications, *e. g.,* phosphorus poisoning, after snake-bites, etc. ; and, finally, in pernicious anæmia and leukæmia.

Hæmorrhages per rhexin cease when the extravascular pressure comes to equal the pressure in the bleeding vessel, or when narrowing of the vessel and coagulation and thrombosis close the rent. *Hæmorrhage by diapedesis* ends with cessation of blood-supply to the bleeding vessel, or when the intravascular pressure is lowered and the vessel-wall restored to its normal state.

The process of diapedesis may be observed in the frog's mesentery or web. If the efferent veins are ligated, the capillaries and veins are seen to be engorged with blood. After a certain time the red blood cells begin to pass from the capillaries and veins (see *Cohnheim,* "Allgem. Path.," i, and *Virch Arch.,* 41 Bd.). *Arnold* (*Virch. Arch.,* 58, 62 u. 64 Bd.) believed that, at the place of exit of the corpuscular elements, spaces between the endothelial cells must exist, and these he designated stomata ; later he found that the supposed openings consist of heaping-up of the cement-substance between the endothelial cells. Under pathological conditions the cement-substance gives way and allows the red blood-cells to pass through.

§ 44. The **sudden closure of an artery** by thrombosis, embolism, ligation, or other means, leads, as has already been stated (§ 39), to stoppage of the circulation beyond the point of obstruction, after the vessel has more or less completely emptied itself by contraction of its walls. At the same time there is an increase of pressure in the vessel from the point of obstruction back to the point of divergence of the nearest branch. If the branches of the artery beyond the point of obstruction have free communication with some unobstructed artery, the latter by becoming dilated may be able to supply a sufficient amount of blood to the affected area to restore the circulation.

If the obstructed artery has no collateral connections through which it may draw its blood-supply, the portion of tissue deprived of blood remains anæmic and dies, giving rise to an **anæmic infarct**. Paren-chymatous organs—for example, the spleen and kidneys—present in infarcted areas a cloudy, opaque, yellowish-white, often clay-colored appearance. (See § 48.)

When the obstructed vessel possesses no collateral anastomoses, as in a **terminal artery**, but if, on the other hand, there is a scanty influx of blood from neighboring capillaries or veins, a **hæmorrhagic infarct**

may be formed. The capillaries of the area rendered anæmic by the obstruction become gradually filled with blood from the capillaries of the adjacent vascular area, and from the veins by retrograde flow. The blood flowing in from adjacent capillaries is under low pressure, which is not sufficient to drive the blood through the obstructed area into the veins. When conditions of pressure become such that a retrograde current sets in from the veins to the capillaries, restoration of the circulation becomes impossible.

The imperfect circulation in the obstructed area, which, through coagulation of the blood in the veins and capillaries, is finally brought to a standstill, leads sooner or later to degeneration and necrosis of the vessel-wall, and to increased permeability. As a result, if the afflux of blood be continued, there occur in the stagnated area *diapedesis of red*
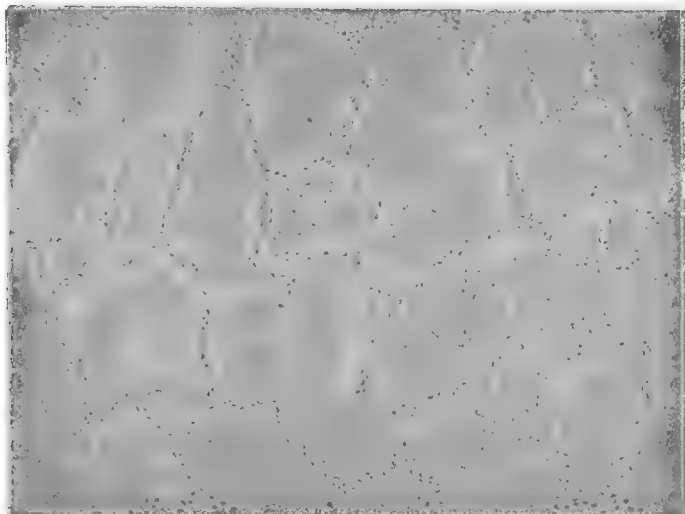
FIG. 30.—Hæmorrhagic infarct of the lung. (Hæmatoxylin and eosin.) Alveoli filled with blood; scattered pale nuclei in the alveolar septa and in the blood of the alveolar spaces, belonging partly to connective-tissue cells and partly to leucocytes. × 40.

cells and infiltration of the tissue with extravasated blood, through which the obstructed area acquires a dark-red color and firmer consistence; a *hæmorrhagic infarct* is thus formed (Fig. 30).

Embolic hæmorrhagic infarcts occur in the lungs (Fig. 30), but are formed *only when there exists passive congestion;* if the pulmonary circulation is normal the disturbances produced by embolism are quickly compensated. In the systemic circulation embolic hæmorrhages are confined almost entirely to the distribution of the superior mesenteric artery, whose branches, though not terminal, possess but few anastomoses. *Anæmic infarcts* occur especially in the *spleen* and *kidneys*. Around the periphery of the anæmic area there is always more or less hæmorrhage, so that the pale infarct is surrounded by a *hæmorrhagic border* or at least by *hæmorrhagic spots*. In obstruction of the cerebral arteries or those of the extremities, or the central artery of the retina, punctate hæmorrhages may occur. In the infarcted area the tissues are wholly or for the greater part dead, and the specific elements of the organ in

particular (Fig. 32, *c, d*) die quickly.   After a time inflammation arises in the neighborhood of anæmic and hæmorrhagic infarcts, with the formation of a cellular (Fig. 32, *f*) or a cellular and fibrinous exudate; this is followed by proliferation of fixed cells, and the dead area is gradually replaced by connective tissue (see Part II. of Chapter VII.).

Literature.

(*Hæmorrhagic Infarction.*)

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Welch: Hæmorrhagic Infarction.   Trans. Assn. Amer. Phys., 1887.

VI. Lymphorrhagia.

§ 45. **Lymphorrhagia** occurs when the continuity of a lymph-vessel is interrupted and lymph is poured into the neighboring tissue.   Since the pressure in the lymph-vessels is low—that is, not greater than in the surrounding tissues—outflow of lymph can occur only when the injured vessel lies on the surface, or when a natural cavity is at hand into which the lymph can flow, or when, through the cause producing the rupture, an open space is formed in the tissues.   For example, escape of lymph together with blood may take place from wounds, but the outflow is stopped by slight counterpressure.   If, after the wounding of a lymphatic, the opening persists, there is formed a **lymph-fistula,** through which considerable quantities may be lost.   Important and often dangerous is *rupture of the thoracic duct,* which sometimes occurs as the result of traumatism, and occasionally as a result of obstruction to the lymph-flow at some point in the lumen of the duct (after inflammation or by the invasion of tumors).   The lymph is poured into the thoracic or abdominal cavity, giving rise respectively, to *chylous hydrothorax* or *chylous ascites;* in rare cases to *chylopericardium.*

It sometimes happens that the urine, as it comes from the bladder, has the appearance of a milk-white, or yellowish, or, through the admixture of blood, a reddish emulsion; and contains albumin and finely-divided fat-droplets. This is known as **chyluria**.   It occurs as an endemic disease in certain tropical regions (Brazil, India, the Antilles, Zanzibar, Egypt) where it is caused by a parasite, the *Filaria Bancrofti,* which inhabits the lymph-vessels of the abdominal cavity and there produces its embryos (*Filaria sanguinis*) ; these, during the repose of the patient in a horizontal position, swarm in great numbers in the blood, and are also found in the chylous urine.   The connection between chyluria and the invasion of the lymph-vessels has not been satisfactorily demonstrated by anatomical investigations; but it is probable that the chyle-like fluid does not come from the blood through the kidneys; but, as a result of obstruction in the lymph-circulation, chyle escapes from ruptured lymphatics of the bladder and mingles with the urine (*Scheube, Grimm*).   In corroboration of this view is the fact that, at autopsy, the abdominal lymphatics exhibit marked dilatation (*Havelburg*), while the kidneys are but little changed; and further, according to an observation made by *Havelburg,* the urine obtained from the ureter showed no admixture of chyle, though chyluria was present at the same time.

The anatomical cause of the non-parasitic chyluria is still unknown.

Literature.

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Lothrop and **Pratt:** Amer. Jour. of Med. Sciences, 1900.

CHAPTER V.

Retrograde Disturbances of Nutrition and Infiltrations of tissues.

§ 46. **Retrograde disturbances of nutrition** are characterized in a general way by *degeneration* of the affected tissue and by *diminution in size* and *disappearance of the individual tissue elements, the functional capacity being at the same time lowered.*

Tissue infiltrations are characterized by the *deposit of pathological substances* which have been formed in the body or introduced from without. The *functional capacity* of the part affected is *diminished.* In some cases, *infiltration is merely a result of degeneration;* in others it may itself *constitute the chief feature* in a *degenerative process.*

Retrograde disturbances of nutrition may effect the body in its fully developed state or during its development and growth; in either case it may lead to abnormal smallness of a part or tissue. In the fully developed body, diminution in size of an organ or tissue due to disappearance of individual tissue elements or to reduction in their size, is designated *atrophy.* If, in the period of development, an organ or part totally fail of development or is represented by rudimentary structures, the condition is known as *agenesia* or *aplasia.* If the development of a part proceed to a certain extent but still does not attain the normal, the condition is known as hypoplasia.

The causes of tissue degenerations and associated atrophy are to be found in those injuries to which the tissues are exposed during life; but atrophy may also depend on intrinsic conditions. The latter is exemplified by tissues which, in old age, reach their physiological limitations and become incapable of nourishing themselves. In certain tissues similar regressive changes occur earlier in life; for example, in the ovary and thymus.

As extrinsic harmful influences which may lead to degenerations should be considered all those agencies mentioned in Chapter I. Disturbances of circulation, lack of oxygen and food supply, and intoxications play a very important rôle. *In the majority of cases degenerations are localized,* so that we may speak of **degenerations of special tissues** or of **special organs.** Not infrequently the **disturbances of nutrition are more general,** so that the entire organism suffers. Thus the picture of a general disease may be produced by a degenerative or atrophic condition of the blood — that is, diminution in the number of red blood-cells (oligocythæmia), at times also deficiency of hæmoglobin (chlorosis), so that a permanent condition of **insufficient blood-supply** or a **general anæmia** is produced, the nutrition of the body being correspondingly impaired.

As the result of diminished ingestion of food, or of disturbed metabolism, and of increased waste of the proteids and fats of the body, there may result a condition of general emaciation and weakness, often

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associated with anæmia, a wasting of the entire body, which is designated **cachexia** or **marasmus.** If under such circumstances it appears likely that certain substances are formed in the body, which, when taken up into the blood and tissue juices, cause contamination or alteration of these, the condition may be spoken of as a **dyscrasia.**

II. Death.

§ 47. All life comes sooner or later to an end — to **death.** When this occurs at an advanced age, without preceding symptoms of disease, it may be regarded as the normal termination. When death occurs prematurely — that is, at an age earlier than the average — and when preceded by symptoms of disease, it must be regarded as pathological. It is obviously impossible to draw any sharp line of separation between physiological and pathological death.

An individual is dead when all his functions have ceased. Death is inevitable at that instant when one or more of the functions indispensable to life has ceased, though it is not necessary that at that moment all should have ceased. Indeed, it often happens, that after life is irretrievably lost, many organs are still capable of function, and it is only after a certain time that all the organs die. *The life of the body passes by progressive cessation of the functions of its different organs into the state of death.*

Cessation of the functions of the heart, lungs, and nervous system results in immediate death of the entire organism. Cessation of the functions of the intestines, liver, or kidneys leads to death after a certain length of time, often measured by days. Destruction of the sexual glands does not endanger the life of the individual, and likewise man may spare one or more of his organs of special sense.

The occurrence of death is usually determined by the last respiration and by stoppage of the heart. With cessation of respiration it is impossible for any organ to remain alive after a certain short period. Stoppage of the heart likewise makes further nourishment of the tissues impossible, in consequence of which the central nervous system is unable to continue.

After death the body may present a variety of appearances. The aspect of the visible portions is largely dependent on the distribution of the blood at the time of death. An abundant supply of blood in the skin gives it a blue-red color, anæmia gives it a pale color. Further, preceding disease may alter the external appearance of the body in different ways.

Within a certain time after death various changes occur in the tissues of the body, which may be regarded as the **absolute signs of death.** In the first place the *temperature of the body falls,* sometimes rapidly, at other times slowly, until it reaches the temperature of the surrounding air. It must be borne in mind, however, that the temperature at times does not begin to sink immediately after death, but first rises somewhat. The rate of cooling of the body depends partly on the character of the body itself, and partly on the nature of its surroundings. The time required may vary from one to twenty-four hours.

The *coldness of the dead body* is termed *algor mortis.*

At the time of death the skin for the greater part becomes pale; but after six to twelve hours, sometimes earlier, bluish-red spots appear on the skin over the dependent parts of the body. These are known as *death-spots* or *livores mortis* (*post-mortem hypostasis*), and are due to the accumulation of blood in the veins and capillaries. They are not found in those parts subjected to the weight of the body. Their number and size depend on the amount of blood in the skin at the time of death. Parts which have been cyanotic during life may retain this appear-

ance after death, especially the head, fingers, and toes. The color of post-mortem hypostasis is usually blue-red; the intensity of the color varies; in cases of poisoning with carbon monoxide it is a bright red.

The weight of the body causes flattening of those muscular parts upon which it rests.

Sooner or later there occurs stiffening and contraction of the muscles, due to coagulation of the contractile substance (*Brueke, Kühne*). This is known as *cadaveric stiffening* or *rigor mortis*. It usually comes on about four to twelve hours after death, but may occur almost immediately or as late as twelve to twenty-four hours. It begins usually in the muscles of the jaw, throat, and neck, and extends from them to the trunk and extremities. After twenty-four to forty-eight hours it usually vanishes, but under certain conditions may persist for several days.

Rigor mortis affects also the smooth muscle fibres; contraction of these in the skin gives rise to the so-called goose-flesh of the cadaver.

Decomposition of the cadaver begins with the disappearance of rigor mortis. Its occurrence is shown by the odor of putrefaction, by changes of color in the skin and mucous membranes, and changes in the consistence of the tissues. The commencement and progress of putrefaction depend partly on the nutrition and the nature of the disease preceding death, partly on the surroundings, especially the temperature. Not infrequently putrefaction may occur in dead areas even before death of the body as a whole. When putrefactive bacteria are present in the body, decomposition may begin immediately after death.

An early sign of decomposition is greenish discoloration of the skin, appearing first over the abdomen. With the progress of putrefaction the unpleasant odor and discoloration increase; gases are formed in the intestine, later in the blood and tissues, which become soft and friable.

Shortly after death the *cornea becomes lustreless, and the eyeball loses its elasticity and shrinks, due to changes in the humors.* If the lids are not closed, the *uncovered portions of the eyeball show the results of drying.* Whenever the skin has lost its epidermis the exposed tissues undergo desiccation.

If the phenomena of life be reduced to a minimum, there may result a condition of **apparent death** which may be mistaken for real death. Though post-mortem hypostasis, rigor mortis, and putrefaction are unmistakable evidences of death, these changes may not take place until some time after death, so that an interval is left during which it may be doubtful whether death has actually occurred. To ascertain the true condition it must be determined by appropriate examination whether the heart still beats, whether respiration still takes place, whether the blood still circulates, and whether the nerves and muscles retain their irritability.

Conditions which simulate death occur under a variety of circumstances, for example, in cholera, in catalepsy, hysteria, after excessive bodily exertion, violent concussion of the central nervous system, sever hæmorrhage, suspension of respiration through hanging, strangulation, or drowning, in certain cases of poisoning, after lightning-stroke, prolonged exposure to cold, etc. The duration of this condition is usually short, but may occasionally be extended.

III. Necrosis.

§ 48. *Local death,* or death of individual cells or groups of cells, is known as **necrosis.** As a result of necrosis the functions of the affected tissue are forever lost.

Necrosis of a cell-group or of an entire organ is only rarely attended by immediately recognizable changes of structure. The slight histological changes which cells undergo during the process of death do not always permit us to determine the cessation of life; nor does the macroscopic appearance of visible portions of the body always inform us when a part has become necrotic.

Necrosis is evident on anatomical investigation only when certain changes in structure have occurred, either coincidently with death or subsequently. Necrosis is shown by immediate histological changes only in a limited number of instances; in all other cases necrosis is followed

by sucn changes after a longer or shorter interval. According to the nature of the tissue-changes it is possible to distinguish different varieties of necrosis.

Histologically, **necrosis of a cell** is shown first by *disintegration and disappearance of the nucleus,* the chromatin breaking up to form small clumps and granules which pass into the cytoplasm and are dissolved (*karyorrhexis*). At other times the nucleus shows *signs of shrinking,* and takes the stain more deeply than under normal conditions (*pyknosis*). In other cases the nucleus *retains its form but loses its staining power,* and then dissolves and disappears (Fig. 31, *c, d*), so that in well-fixed and well-stained preparations no trace whatever can be found (*karyolysis*). Thus, in an anæmic infarct of the spleen or kidney the nuclei of the spleen and kidney cells are lost soon after the death of the tissue (Fig. 32, *c, d, f, g*). At the same time the affected area becomes pale, cloudy, yellowish-white, or cream-colored; so that the presence of necrosis may be recognized by the naked eye.

FIG. 31.—Necrosis of the epithelium of the urinary tubules in icterus gravis. (Müller's fluid, gentian violet.) *a,* Normal convoluted tubule; *b,* ascending portion of the loop; *c,* convoluted tubule with necrotic epithelium; *d,* convoluted tubule with only a part of its epithelium necrotic; *e,* normal stroma with blood-vessels. × 300.

The *protoplasm* of dying cells sooner or later undergoes *changes* which, according to the mode of death, may begin before the cells die, or take place only after the cells are dead. The kind of change is dependent on three factors: the nature of the cells themselves, the character of the destructive influence, and the amount and character of the fluids surrounding and infiltrating the cells. Amœboid cells usually assume a *globular form* after death. Cell-bodies, rich in protoplasm, often become, before or after death, markedly *granular,* less frequently *homogeneous* and *lumpy* (Fig. 31, *c,* and Fig. 32, *e*). Through the taking-up of fluid the protoplasm or even the nucleus may become *swollen* and show *drops of fluid (vacuoles)*; and this may lead to breaks in the continuity of the protoplasm (*plasmoschisis*). Not infrequently as a result of plasmochisis *portions of the cell may be extruded* or *cut off.* The end of all these changes is *disintegration of protoplasm and nucleus into granular masses,* the process often being accompanied by the formation of fat.

The injurious influences which give rise to necrosis may be divided into five groups. The first two include those which destroy the tissue directly — **mechanical and chemical forces.** A third group **comprises those of thermal character.** Elevation of the temperature of a tissue to 54°–68° C. for any length of time leads to its death. Higher temperatures act more quickly. Refrigeration to low temperatures likewise can be borne but a short time. A fourth group is caused by **infection.** A fifth group is caused by **cessation of nourishment and**

oxygen to the tissues, and is known as **ischæmic necrosis** or **local asphyxia** (Fig. 32).

All those factors which *affect the circulation in any part* and lead to *stoppage of the blood-supply* — such as thrombosis, embolism, ligation, pressure, etc., may lead to necrosis of tissue. Not only permanent cessation of circulation, but also temporary stoppage lasting beyond a certain time, leads to death of the affected tissue. Whether hæmorrhage occurs in such cases is immaterial, and influences only the appearance
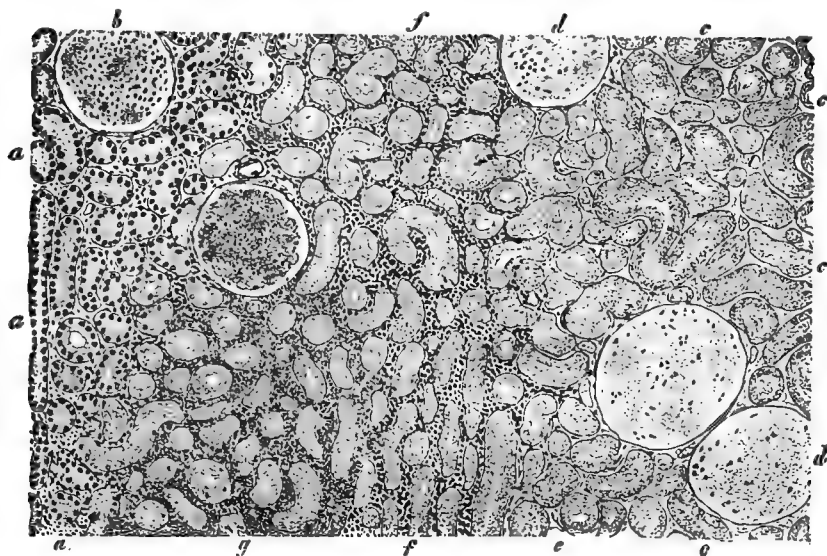
FIG. 32.—From the edge of an anæmic infarct of the kidney. (Müller's fluid, hæmatoxylin, and eosin.) *a*, Normal kidney tissue; *a₁*, normal kidney-tubules with stroma infiltrated with leucocytes; *b*, normal glomerulus; *c*, necrotic tissue without nuclei, showing granular coagula in the tubules; *d*, necrotic swollen glomerulus with few nuclei; *e*, tubules without nuclei in a stroma still containing nuclei; *f*, necrotic tissue with cellular, *g*, with hæmorrhagic infiltration. × 50.

of the part. *Hæmorrhagic infarction* has, therefore, the same significance as *anæmic necrosis associated with hæmorrhage*.

When death follows quickly on the action of an injurious agent, it is spoken of as **direct necrosis**. When it occurs slowly and is preceded by tissue-degenerations it is designated **indirect necrosis** or **necrobiosis**.

Mechanical, chemical, thermal, and infectious agents may act coincidently, or separately, one after the other. When the tissue is damaged by any one of the group, the blood often suffers changes which lead to stasis and coagulation in the capillaries, as well as in the veins and arteries, and in this way the circulation is arrested.

Whether injury will cause necrosis of tissue depends, not only on its nature and severity, but also on the condition of the tissue at the time of injury. A tissue whose vitality has been lowered as the result of long-continued disturbances of circulation, changes in the composition of the blood, etc., dies more easily than the normal. In typhoid fever relatively slight pressure on the trochanters, elbows, sacrum, heels, etc., may suffice to bring about necrosis of the skin and

subcutaneous tissues. Such forms of necrosis are known as **marasmic necrosis** or **marasmic gangrene,** and as **decubitus** or **decubital necrosis.**

The **course of necrosis** is dependent on the character of the affected tissue, its location, the manner of its death, and the cause of the necrosis. Further, the amount of lymph and blood in the tissue, the opportunity afforded for the access of air and putrefactive organisms, together with preceding tissue changes are of significance in determining the character of the necrosis.

As the **result of necrosis of certain tissues,** there always develops *inflammation of greater or less intensity in the surrounding parts.* (Fig. 32, *f*). This reactive inflammation is most marked when the necrotic area becomes gangrenous. The necrotic area becomes isolated or sequestrated; this process is spoken of as a *sequestrating or limiting inflammation,* and the dead area thus shut off is called a *sequestrum.* A more detailed description of these inflammatory processes will be found in Chapter VII.

Five chief **sequelæ** of necrosis may be distinguished: 1. The dead tissue may be removed by *absorption,* or *cast off,* and *its place taken by normal tissue (regeneration).* 2. The dead tissue is similarly removed, but instead of normal tissue being restored, the defect is filled wholly or in part by connective tissue, so-called cicatricial tissue. 3. The necrotic tissue is cast off or liquefied, the defect is not filled in and an *ulcer* remains. Should this heal without regeneration of the lost tissue there remains a *scar.* 4. The necrotic tissue is partly absorbed, but a portion remains as a *sequestrated mass* which not infrequently becomes *calcified* and *surrounded by a connective-tissue capsule.* 5. The fifth sequel of necrosis is *cyst-formation.* The necrotic area becomes encapsulated by connective tissue, the dead tissue becomes liquefied, and the space filled with fluid. This sequel of necrosis occurs most frequently in the brain.

By many writers there is recognized besides these forms of necrosis a special variety designated **neuropathic necrosis,** that is, necrosis resulting from a lesion of the central or peripheral nervous system. By some the cause of such necrosis is referred to a lesion of the trophic nerves, while others refer it to disturbances of circulation, pressure, and mechanical injury of anæsthetic and paralyzed portions of the body. According to observations made on men, as well as in experiments on animals, injuries and disturbances of circulation play the most important rôle in the production of this form of necrosis, and can never be wholly excluded.

The time required to kill tissue by shutting off the circulation varies with different tissues. Ganglion-cells, kidney epithelium, and liver-cells die quickly, while surface epithelium and connective tissue may live for hours. Epidermis under certain conditions may remain alive for a number of days, and still retain its power of proliferation (see Transplantation).

§ 49. According to the condition of the tissue, **four chief forms of necrosis** may be distinguished: *coagulation-necrosis, caseation, liquefaction-necrosis,* and *gangrene.*

Coagulation-necrosis is characterized by coagulation, either *extracellular,* in the fluids about the cells; or *intracellular,* leading to changes in the cells.

Coagulation-necrosis with extracellular coagulation is exemplified by both intravascular (Figs. 10, 13) and extravascular *coagulation of the blood,* inasmuch as this phenomenon constitutes death of the blood; and in fact destruction of cells does occur. Further, there may be considered as belonging to this class the various forms of coagulation which occur

in inflammations, on the surface and in the interior of the tissues (see Chapter VII.) and which are characterized by the formation, in some cases, of stringy fibrin, in other cases by granular or hyaline masses of coagula.

Intracellular coagulation occurs when dead cells are infiltrated with coagulable lymph. The cells lose their nuclei and present either a granular (Fig. 31, *c, d,* and Fig. 32, *c, d, e*) or hyaline appearance. They remain in this condition for a time and then break down into granules and are dissolved.

This phenomenon is most frequently observed in anæmic, toxic, and thermal necroses, for example, in anæmic infarcts of the kidney (Fig. 32) and of the spleen, also in many inflammations which are associated with infiltration of the tissues, due to exudation from the blood-vessels. In the necrosis of striped muscle, which is of frequent occurrence in typhoid fever and other infections, the contractile substance acquires a waxy appearance and breaks up into hyaline lumps.

The necrotic tissue of anæmic infarcts is yellowish-white, or cream-colored. Muscles containing many dead fibres in a state of hyaline coagulation are pale red, and of dull lustre, resembling fish-flesh. Inflamed tissues undergoing coagulation necrosis are cloudy, opaque, and grayish-white; but the color may undergo marked changes through admixture of blood or imbibition of bile, as in the intestine, for example.

The structure of a tissue which is the seat of coagulation-necrosis, may still be recognized if only the more delicate parts have been destroyed. When all parts have been changed, the tissue may be converted into a structureless, hyaline, or granular mass, containing no nuclei or few. This change takes place often in the necrosis of inflamed tissues which are infiltrated with exudate. There frequently may be demonstrated in these necrotic areas intercellular stringy fibrin; occasionally in anæmic infarcts, but more often in inflammatory necroses.

Caseation is a form of coagulation-necrosis, and is characterized by a cheesy appearance. The dead tissue resembles yellowish-white, hard cheese, or raw potato, or is white, soft, dry or moist, resembling thick cream.

Typical caseation occurs most frequently in *tubercles* and represents the end of the retrogressive changes in this condition. It also occurs in syphilitic granulomata and in cellular tumors; inflammatory exudates may also become changed into cheesy masses.

The process of caseation takes place gradually, and is to be regarded as a form of **necrobiosis.** The cells are changed successively into non-nucleated, homogenous or lumpy masses, which disintegrate and break up into granules. At the same time there often appears between the cells a delicate, thread-like or hyaline substance, sometimes forming a framework around the cells or at other times more lumpy or granular — the so-called " *fibrinoid substance.*" *Typical fibrin* (Fig. 33, *a*) staining deep blue with Weigert's fibrin stain is often present. It may be assumed that both represent coagulation-products of fluid which has escaped from the blood-vessels.

Through progressive cleavage and disintegration of the dead cells, and of the fibrinoid substance and fibrin, the tissue is ultimately reduced to a finely granular mass, in which no traces of the original structure can be perceived.

The cheesy metamorphosis of fibrino-cellular exudate. which is found especially in the lungs in the neighborhood of tubercles, is similarly brought about by disappearance of the nuclei, and the disintegration of cells and fibrin into a non-nucleated granular mass.

The granules of the soft cheesy masses in tuberculous and non-tuberculous foci are chiefly albumin particles, more rarely fat-droplets. The fate of such masses may be *liquefaction* and *pultaceous softening, absorption, desiccation or calcification.*

Colliquation or **liquefaction-necrosis** is characterized by the fact that the *necrotic parts become dissolved in the fluids of the tissues.* The dissolution may be accomplished by swelling and liquefaction, or by
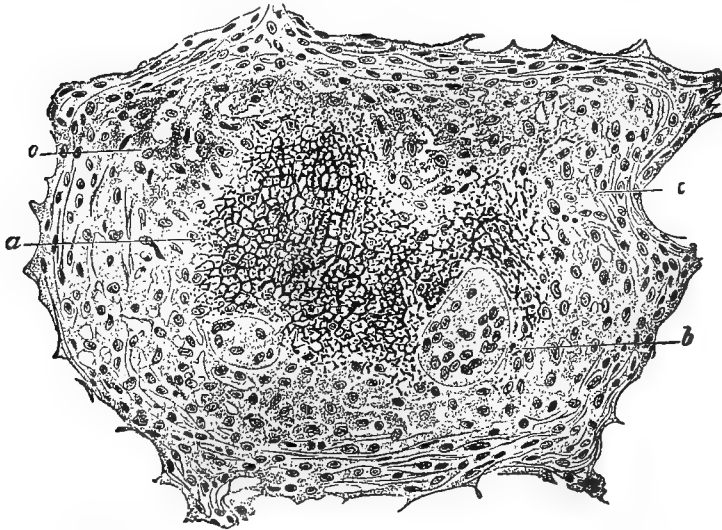
FIG. 33.—Fibrin-containing tubercle from the lung. (Alcohol, hæmatoxylin, fibrin stain.) *a*, Fibrin; *b*, giant-cell; *c*, cellular portion of the tubercle. × 300.

breaking up of the tissue-elements, or by a combination of these processes. Thus, in burns of the second degree the cells of the epidermis, which have been killed by the heat, become dissolved in the fluid exuding from the papillæ (Fig. 34, *d, f*). In the case of anæmic infarcts of the brain the *necrotic* brain-substance undergoes softening, and becomes converted into a milky, pultaceous mass and the products of destruction disintegrate into smaller particles, which, either free or enclosed in cells, become absorbed or dissolved. In suppurative processes necrotic tissue is dissolved in fluids exuded from the blood-vessels. Necrosed areas in the mucosa of the stomach become dissolved through the digestive action of the gastric juices.

Coagulation and *liquefaction* may follow or precede each other. For example, the products of coagulation may again become dissolved. In gangrenous blebs produced by solution of epithelial cells coagulation may occur, the products of which are later dissolved. Necrotic foci arising in the course of granulomata or other inflammations, often become liquefied.

In both *coagulation* and *liquefaction* of tissues the process depends on the **action of ferments,** which are derived from living protoplasm or are contained in the dead tissue. The liquefaction of tissue by ferments is designated **autolysis.** The action of **autolytic ferments** also takes place in portions of tissue that have been kept outside the body in fluids that inhibit the growth of bacteria, and such liquefaction is attended by the formation of various products of decomposition.

The changes described above as occurring in dead or dying tissues are not the only ones which take place during tissue-destruction. They are the chief types which occur in the course of relatively rapid necrosis. Many of the tissue-degenerations described in the following paragraphs lead, not infrequently, to death of tissue, and consequently must be regarded as belonging to the processes classed as *necrobiosis.* Granular, fatty, mucous, and hydropic degeneration often end in destruction of cells; and the same result may be reached in hyaline and amyloid transformation of connective-tissue, in that not only the ground-substance is permanently altered, but the cells also die.
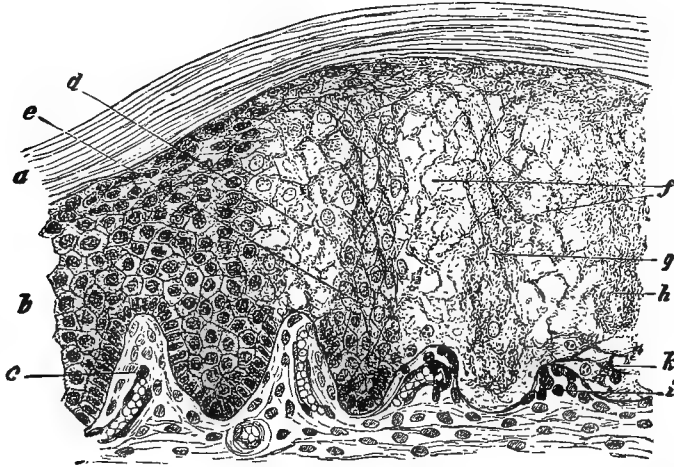
Fig. 34.—Blister of cat's paw, caused by hot sealing-wax. (Alcohol, carmine.) *a,* Horny layer of the epidermis; *b,* rete Malpighii; *c,* normal papilla; *d,* swollen epithelial cells whose nuclei are in part visible, and in part have disappeared; *e,* epithelial cells lying between the papillæ, the upper ones swollen and elongated, the lower ones preserved; *f,* total liquefaction of the epithelium; *g,* swollen cells of the interpapillary cell-masses, which have lost their nuclei; *h,* a similar cell-mass which has been completely destroyed, and raised from the basement-membrane, by the coagulated subepithelial exudate *k; i,* flattened papillary body infiltrated with cells. × 150.

§ 50. Under **gangrene** may be classed those forms of necrosis in which tissue, partly through exposure to the air, partly through the agency of bacteria, suffers changes similar in appearance to those occurring in burned tissues. If necrotic tissue through exposure to air loses water by evaporation and becomes dry, the condition is designated **dry gangrene** (*gangræna sicca*) or **mummification.** When the dead part remains moist, the terms **moist gangrene** (*gangræna humida*) or **sphacelus** may be applied. If through the agency of bacteria there occurs *foul-smelling putrefaction,* the condition is known as **putrid gangrene** (*gangræna fœtida*). Development of gas-bubbles as a result of putrefactive changes leads to **emphysematous gangrene** (*gangræna emphysematosa*).

Moist gangrene and putrid gangrene are in general identical, since bacteria develop only in moist tissues. Nevertheless dry gangrene is not infrequently putrid, since bacteria may develop in the tissue before drying takes place. Dry gangrene may also develop from moist gangrene, or through the absorption of water become changed into the latter.

When gangrenous tissue contains a large amount of blood, it appears black, dark brown, or greenish-black in color, and is called **black gangrene**. If, on the other hand, the dead tissues are anæmic, the condition is sometimes spoken of as **white gangrene**, although the expression is often inappropriate, since there is more or less discoloration of the dead part.

In gangrene of superficial parts of the body, there may be distinguished, according to the temperature of the part, *cold* and *warm gangrene*, the latter designation being used when the area is kept warm by the blood flowing through neighboring tissues.

Gangrene may be caused by external injuries, heat, cold, corrosives, crushing, pressure, infection, etc., as well as by disturbances of circu-

FIG. 35.—Dry gangrene of the toes, due to calcification, narrowing, and obliteration of their arteries.

lation, characterized by interference with the arterial inflow or the venous exit, or both.

Gangrene due to disturbance or arrest of the circulation occurs not infrequently in old people (*senile gangrene*), involving the extremities, particularly the toes, feet, and legs. It is usually of the dry variety, and is dependent partly on general disturbances of the circulation and partly on disease of the arteries of the extremities (arterial sclerosis, thrombosis, embolism) (Fig. 35). The dying parts appear bluish-black as a result of venous stasis.

Gangrene from cold affects chiefly the tips of the extremities — nose, and ears — and is characterized by changes similar to those described above.

Gangrene from heat is confined to the area directly affected by the heat.

Pressure-gangrene or **decubitus** (*bedsore*) occurs in marasmic individuals, most frequently over the sacrum and heels, both of which are exposed to pressure when the individual lies on his back. The bedsore begins with the formation of bluish-red spots, within whose area the tissue dies, and through the agency of bacteria undergoes decomposition and finally disintegrates. The gangrenous area may be of large extent, especially over the sacrum; the bone may be laid bare through destruction of the overlying soft parts.

Toxic gangrene occurs in ergot poisoning as a result of the contraction of the small vessels and formation of thrombi. The tips of the extremities are usually affected. The prolonged application of dilute solutions of carbolic acid to wounds of the extremities not infrequently produces local death of tissues.

Infectious gangrene occurs in the skin and subcutaneous tissue, and may be associated with gas-formation particularly in infections produced by or associated with the bacillus aerogenes capsulatus and related micro-organisms. Infections associated with putrid gangrene may occur in the internal organs, chiefly the lungs and intestines.

So-called **neuropathic gangrene** occurs when a tissue affected with either sensory or motor paralysis is wounded or subjected to continued pressure. It is dependent partly on circulatory disturbances and partly on infection. Gangrene resulting from withdrawal of the influence of trophic nerves has not yet been demonstarted. **Symmetrical gangrene** which affects corresponding parts of the extremities and has been regarded by many as a neuropathic disease, is probably dependent on changes in the blood-vessels; likewise, the perforating ulcer of the foot (*mal perforant du pied*), which begins as a callosity following mechanical influences, and is characterized by an accompanying gangrene which rapidly penetrates into the deeper tissues, is dependent on the closure of an artery of the foot.

In moist gangrene the tissues break down with varying rapidity, the fasciæ resisting the longest. If the gangrene comes to a standstill, the dead tissue becomes sequestrated through a zone of demarcation — that is, becomes separated from the living tissue and under favorable conditions may be thrown off. In the case of necrotic portions of bone a long time is required for sequestration. Extension of gangrene leads sooner or later to death, especially if toxic substances or bacteria are taken into the blood or lymph.

There is a variety of gangrene which occurs frequently, although not exclusively, among Polish and Russian Jews, most commonly in young adults, and between the ages of 25 and 35 — hence the designations "die Hebraische krankheit," presenile or juvenile gangrene. Buerger, from a study of the pathological changes in the vessels of this disease has designated the condition thrombo-angeitis obliterans. The patients complain of indefinite pains in the feet, in the calf of the leg or in the toes, and of a sense of numbness or coldness whenever the weather is unfavorable. One or both feet may be markedly blanched, cold to the touch, and pulsation in the dorsalis pedis or posterior tibial artery may be wanting. After the lapse of months — sometimes years — a blister, bleb, or ulcer develops near the tip of one of the toes, usually the big toe, frequently under the nail, and when this condition ensues, local pain becomes intense. Dry gangrene of the involved toe now occurs and, indeed, the entire foot may share in the process of death. The exciting cause of the changes in the vessels is totally unknown. (Buerger, American Journal Medical Sciences, 1908.)

IV. Hypoplasia, Agenesia, and Atrophy.

§ 51. **Hypoplasia** may affect the body as a whole or single organs or parts of organs, either during intra-uterine or post-embryonal development.

When the entire skeleton or the greater part of it is under-developed, and especially if the bones do not attain their normal length, the affected individual is abnormally low in stature, and is called a *dwarf* (Figs. 36 and 37). The individual parts may be well proportioned (Fig. 36), or

asymmetrically developed (Fig. 37). For example, the trunk may be of normal size, while the extremities are short (Fig. 37) ; or both the trunk and the extremities may be abnormally small, while the head is of normal size, and consequently appears relatively large for the body. When the vice of development affects individual parts of the skeleton, or is
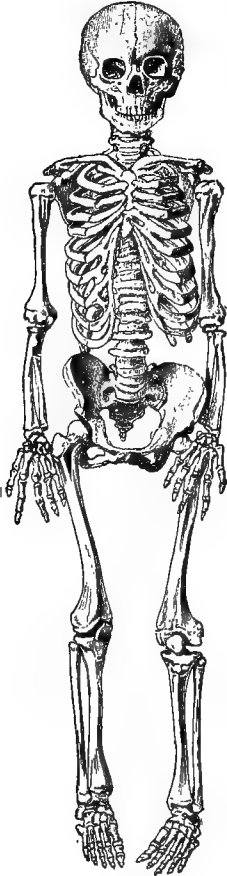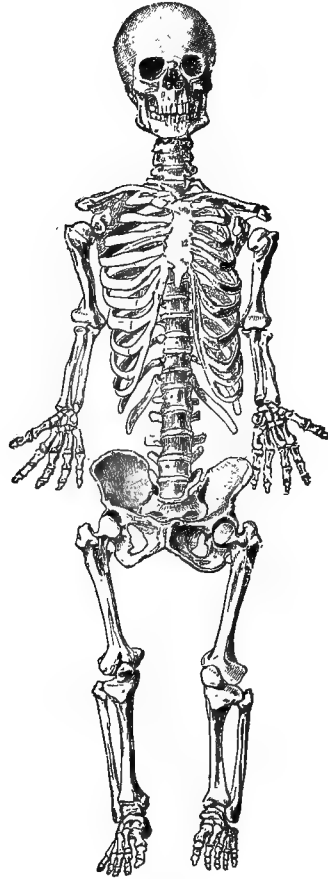
<p align="center">Fig 36.   Fig. 37.</p>

Fig. 36.—Skeleton of a female cretin, thirty-one years of age, 118 cm. in height, with klino-cephalic skull. The cartilage sutures of the diaphyses of the long bones and pelvic bones still show; as does also the frontal suture. The individual parts of the skeleton are, on the whole, in the proper proportion, the upper extremities alone being relatively short.

Fig. 37.—Skeleton of a female dwarf of fifty-eight years of age, 117 cm. in height, with very short extremities, and long trunk. The cartilage sutures are still present; the articular ends of the bones are thick.

more marked in certain parts than elsewhere, stunting results. For example, defective development of the cranium gives rise to *microcephalus* and *micrencephalus;* defective development of the humerus results in shortening of the arm; and through hypoplasia of the lateral masses of the sacrum the transverse diameter of the pelvis becomes diminished.

The central nervous system and the genito-urinary tract in particular suffer stunting of development, although the intestines, heart, lungs, liver,

etc., do not escape similar disturbances of growth. For example, the entire brain, or one of the hemispheres, may fail of development. The intestine may be represented by a thin canal or by a solid cord. The uterus not infrequently remains in an undeveloped state, and occasionally the entire generative apparatus may remain undeveloped throughout adult life. Marked hypoplasia of the kidney is not rare.

The tissue composing hypoplastic organs or parts of organs, though of less bulk than normal, may present no other abnormalities of structure. In certain cases hypoplasia may be *associated with agenesia of individual parts*. Thus, in hypoplasia of the ovary the development of

FIG. 38.—(Bellevue Hospital.) Excessive atrophy of muscle tissues.

ova and the ripening of follicles may fail; in hypoplasia of the brain there may occur defective development of the ganglion-cells and nerve-fibres, at times portions of the brain may consist of membranous masses in which no ganglion-cells are present. In hypoplasia of the lung there may be complete failure of development of the alveoli, so that the lung consists entirely of bronchi embedded in connective tissue.

§ 52. **Atrophy** *is diminution in the size of an organ due either to reduction in size or disappearance of its individual elements.* It may occur at any period of life, and is a common result of many pathological processes. Within certain limits it may be regarded as a *physiological phenomenon,* in that in old age there constantly occurs a retrograde change in all the organs, associated with diminution in size. Certain organs

undergo atrophy with partial or total loss of functional power before old age, for example, the thymus, which atrophies even before the end of the period of growth; and the ovary, a part of whose ova are discharged during the period of sexual activity, the remainder being destroyed.   The lymphoid tissues suffer atrophy at a comparatively early age, the bones and muscles at a later date.

Atrophy of an organ is characterized chiefly by diminution in size. In atrophic conditions of the muscles the affected portions of the body become smaller, and in marked cases the extremities appear as if consisting of skin and bones.   When atrophy of an organ is uniform, its normal shape is preserved; but if the atrophy progresses more rapidly in certain parts than in others, the surface may show local depressions and cicatricial contractions, so that, for example, the liver or kidney, may present a knobbed or granular appearance.   When tissues which are undergoing atrophy are prevented from contracting, as in the case of the bones and lungs, the external form is preserved.   In bone, the medullary spaces and Haversian canals become enlarged, and a condition re-
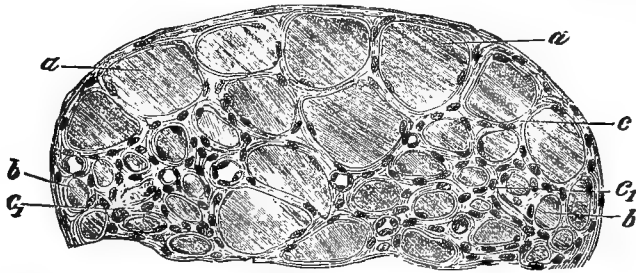
Fig. 39.—Section of an atrophic muscle, from a case of progressive muscular atrophy. (Müller's fluid, Bismarck brown.)   a, Normal muscle-fibres; b, atrophic muscle-fibres; c, perimysium internum, the nuclei of which, at c_1, seem to be increased in number.   × 200.

sults which is known as *excentric atrophy* or *osteoporosis*.   In the lungs the alveoli become confluent into large air-spaces as the result of disappearance of the intervening walls.

In atrophy of glands and muscles there frequently occurs a change of color, though this is of secondary importance.   Either the *normal pigment* of the organ is brought out *more distinctly* by atrophy, or associated with the atrophy there is a *deposit of pigment* (*brown* or *pigment atrophy*), or the change of color may be dependent on the blood-content of the atrophic tissue.

The diminution in size of atrophic organs is the result of diminution in size and disappearance of the histological elements composing them. In the majority of organs, particularly glands, muscles, and bones, the cells which perform the special function of the affected organ, are affected in atrophy to a greater degree than the connective-tissue framework.   Indeed, it may be observed that the connective-tissue elements are preserved, or even increased in number, while the more highly specialized elements have disappeared.   Thus, in atrophic muscle the contractile substance within the sarcolemma may disappear to a great extent without the occurrence of any atrophy of the connective tissue between the muscle-bundles.   The nuclei of the connective tissue may even be increased in number.

In atrophy of the kidney the epithelial cells of the tubules (Fig. 40, *a*) become smaller and may vanish so that the tubules collapse. Likewise, the epithelium of the glomeruli is lost and the capillaries are obliterated.

The same thing occurs in simple atrophy of the liver, in that many of the cells of a lobule may disappear without any perceptible decrease of the supporting reticulum. Likewise the ganglion cells of the brain and spinal cord may atrophy without the neuroglia being diminished. Not infrequently the latter may become increased.

In atrophy of bones the true bone-tissue becomes diminished. In atrophy of the bone-marrow the total mass of marrow-cells is diminished. The supporting cells may take up an increased amount of fat; but, on the other hand, the fat in the cells of the marrow may vanish, so that spaces filled with fluid are formed between the supporting cells.
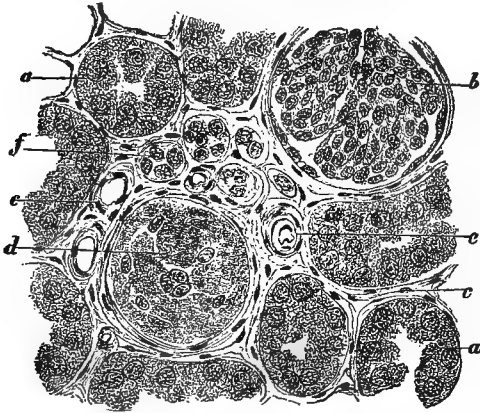
FIG. 40.—Senile atrophy of the kidney. (Alcohol, alum-carmine.) *a*, Normal urinary tubules; *b*, normal glomerulus; *c*, stroma with blood-vessels; *d*, atrophic and obliterated glomerulus; *e*, small artery, with thickened intima; *f*, atrophic and collapsed urinary tubules. × 200.

Atrophy may take place without any apparent change of structure in the tissue-elements (Fig. 39), the condition being reached through loss of volume of the individual parts. Both the cell-body and nucleus become smaller; the latter change may be observed particularly in the liver in starvation. This form is known as **simple atrophy,** and is to be distinguished from the **degenerative atrophies,** in which the *tissue-elements show changes in structure.* Thus a cell may become granular, and undergo fragmentation, or may swell and liquefy, or there may be formed in the cell drops of fat or mucus; all of these changes signifying degenerative conditions of the protoplasm. Degenerative changes can occur at the same time in the nuclei, as shown by fragmentation, distorted shape, clumping of chromatin or its diffusion into the protoplasm, swelling and liquefaction of the nucleus. These processes lead ultimately to disappearance of the nucleus and destruction of the cell.

According to their genesis the several **forms of atrophy** may be classed as **active** or **passive.** In the former the cell is no longer able to make use of the food brought to it; in the latter the food is either not supplied in sufficient quantity or proper form, or substances are brought to the cells which impair their function. Active atrophy is part of the involution of old age, but occurs under pathological conditions, especially in nerves, glands, and muscles whose function is in abeyance.

The clinician prefers another classification of atrophy; namely, senile atrophy, atrophy due to impaired nutrition, pressure atrophy, atrophy of disuse, and neuropathic atrophy.

Senile atrophy is partly active, and partly passive, in that it is not simply the result of the diminishing vital energy of the cell, but also

depends on narrowing and obliteration of the vessels conveying nourishment to the cells. It may occur in all the organs, but is often more marked in one than in another, notably in the bones, kidneys, liver, brain, and heart, all of which may undergo marked loss of volume.

Atrophy due to impaired nutrition may result from insufficient supply of food to the body as a whole, or from extensive loss of fluids. In these cases the whole body is affected, though the fat, blood, muscles, and the abdominal organs suffer to a greater extent than the remaining tissues. Local atrophies may result from local disturbances of circulation, and are frequent sequelæ of *diseases of the arteries* in which the vessel lumen is narrowed. Further, they are of frequent occurrence in or after inflammatory processes; in these cases the condition is not of the nature of simple atrophy, but of *degenerative changes* leading to the death of cells and tissues.

Pressure-atrophy occurs when a tissue is subjected for a length of time to moderate pressure. It depends partly on direct injury to the tissues and partly on disturbance of the circulation. The most typical examples are atrophy of the liver caused by the pressure of the edge of the ribs on the organ due to tight-lacing ("corset-liver"), and the disappearance of bone following the pressure of an aneurism, tumor, or accumulation of fluid.

Atrophy of disuse occurs in the muscles, glands, bones, skin, and other tissues. In muscles and glands the atrophy is active, the nutritive processes diminishing as the result of lessened functional activity. In the other tissues the atrophy is largely dependent on the lowering of nutrition of the disused parts, though a change in the power of assimilation of the cells cannot be excluded. When the inactivity occurs during the period of development the condition is to be regarded as hypoplasia, though no sharp line can be drawn between hypoplasia and atrophy, since in the former there may also be disappearance of structures which had undergone a certain degree of development.

Neuropathic atrophy is a result of diseased conditions of the nervous system.

For example, after destruction of the anterior horns or the motor roots of the spinal cord, there follows atrophy of the corresponding nerves and muscles. After injury of peripheral nerves the skin often becomes atrophic. According to many authors, disease of the nerve-trunks of one side of the face is followed by *unilateral neuropathic facial atrophy,* but by others (Möbius) the neuropathic nature of this condition is contested. Unilateral affections of the brain in fœtal life or during childhood may lead to atrophy of the opposite side of the body (*congenital and infantile hemiatrophy*).

V.   Cloudy Swelling and Hydropic Degeneration.

The term **cloudy swelling** or *parenchymatous* or *granular degeneration* is applied to that form of cell-degeneration which is characterized histologically by swelling and enlargement of the cells due to the formation in the protoplasm of free granules, which according to their microchemical properties (solubility in acetic acid, insolubility in alkalies and ether) are to be regarded as albuminous bodies. The epithelial cells of the kidney and liver (Fig. 41), and the heart-muscle frequently show this degeneration, acquiring a cloudy appearance, as if covered with

dust, while at the same time their normal structure and form are lost. Thus, in cloudy swelling of the kidney-epithelium the rod-like markings of the protoplasm are lost (Fig. 42, *a*), as are the cell-processes projecting into the lumen of the tubules. The cells (*b. c. d*) are swollen, plump and granular. This change is to be regarded as a *disorganization of protoplasm* following absorption of fluid, and leads to partial separation of the solid and liquid constituents of the protoplasm. At the same time the *nucleus swells and undergoes disorganization.*

FIG. 41.—Cloudy swelling of liver-cells (scraping from the cut surface of the liver of a man dying of septicæmia, examined in normal salt solution.) × 350.

Recovery is possible at a certain stage of the process, and the cells may be restored to normal. In other cases the cell-body is destroyed, breaking into granular fragments. Fatty degeneration often succeeds cloudy swelling.

Cloudy swelling may occur in the cells of any of the parenchymatous organs, as the liver, kidneys, or heart, during the course of infectious diseases, particularly scarlet fever, typhoid, smallpox, erysipelas, diphtheria, septicæmia, etc. The affected organs present a cloudy, often gray appearance; in marked cases the organ may appear cooked, the blood-content is slight, the consistence doughy, and the details of structure are lost.
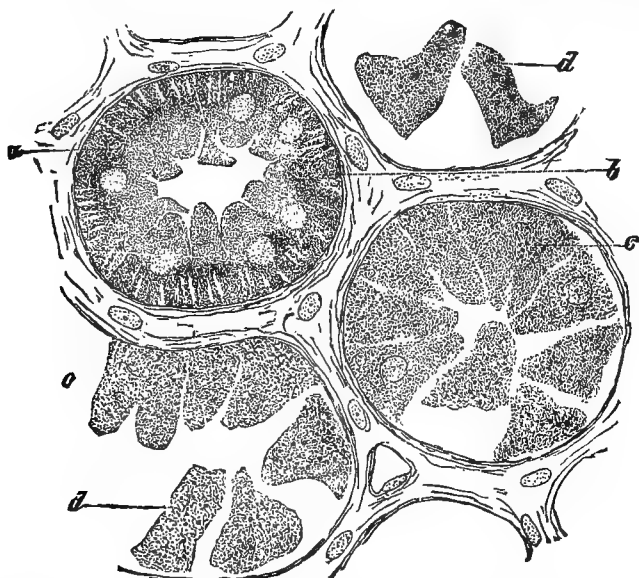
FIG. 42.—Cloudy swelling of kidney epithelium. (Chromic acid, ammonia, glycerin.) *a*, Normal epithelium; *b*, beginning cloudy swelling; *c*, advanced stage of cloudy swelling; *d*, desquamated degenerated epithelium. × 600.

It is not improbable that autolytic processes (see paragraph 49) play a rôle in parenchymatous degeneration (*Landsteiner*). *Orgler* regards it as autolysis accompanied by increase of the water-content. The granules which become visible and show double refraction he regards as protagon, which, during autolysis, is either preserved because of its slight solubility or during the course of the process is precipitated in the form of granules.

According to the investigations of *Symmers* (Jour. Exp. Med., 1907), the process of *autolysis* results in morphological changes, not only in certain fixed tissue cells, but in those of the blood. The changes are characterized mainly by solution of the hyaloplasm with exposure of the spongioplastic network and retention of the cell membrane, giving the cell a finely reticulated appearance. The effects of autolysis are particularly noticeable in the liver, where it sometimes occurs focally, at other times over a wide distribution. Extensive autolytic degeneration of the liver not infrequently is to be observed in the toxæmias of pregnancy and in patients dead of uræmia.

§ 54. **Hydropic degeneration** is that form frequently observed in cells of different kinds, whereby they become swollen through the imbibition of fluid — it is an intracellular œdema. When epithelial cells undergo this change the contents appear clear, the granules of the protoplasm are pressed apart by the fluid, often crowded into a ring at the periphery; the cells thus resemble plant-cells. Globules of clear
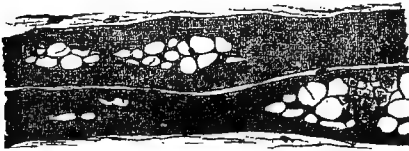
FIG. 43.—Hydropic degeneration of muscle-fibres from the calf muscle in chronic œdema of the leg. (Flemming's solution, safranin.) × 45.
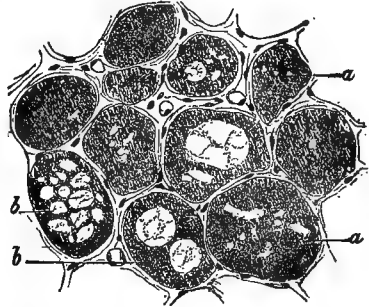
FIG. 44.—Transverse section of a muscle-bundle showing hydropic degeneration of its fibres. (Müller's fluid, hæmatoxylin.) *a*, Muscle-fibre with small drops of fluid; *b*, muscle-fibre with large drops. × 66.

fluid may often be formed in the cells. The nucleus swells and becomes changed to a bladder-like structure containing clear fluid. In muscles showing hydropic degeneration clear droplets of fluid appear between the fibrillæ, pushing the latter apart (Figs. 43 and 44, *a, b*). Through the abundant formation of such drops the muscle fibres may acquire in places a foamy appearance (Fig. 43). At first, the muscle fibres between these drops remain preserved, but finally undergo fragmentation and liquefaction.

Hydropic degeneration of cells may be the result of œdema (Figs. 43 and 44); it occurs in inflammatory foci (Fig. 34) and in tumor-cells. In inflammation the degenerative character of the process is more marked than in simple œdema; and complete liquefaction of the cells may result. In œdema the cells, in spite of their hydropic condition, may remain alive for a long time.

VI. Fat Deposit and Fatty Degeneration.

§ 55. **Fat,** in a form that can be demonstrated microscopically, is widely distributed through the human and animal organism. It appears most prominently in the subcutaneous and subserous tissues and bone-marrow; in these regions adipose tissue develops at a certain time during embryonal life or in childhood. Less prominent, and in part visible only on microscopic examination, is the fat present in various glands, in ganglion-cells, leucocytes, surface epithelium, duct epithelium, endothelium, etc.

The **fat of adipose tissue** occurs in the connective-tissue cells in which it is deposited in the form of droplets that often become confluent, so that the fully developed fat-cell appears as a spherule surrounded by a cell-membrane and containing a nucleus. In preparations mounted in Canada balsam the fat-drop is represented by a clear vacuole (Fig. 46, *c*) the fat itself having been dissolved by the ether used in the process of preparation. Sudan III. and Scharlachroth stain fat a yellowish-red (Fig. 45), while treatment with osmic acid, which
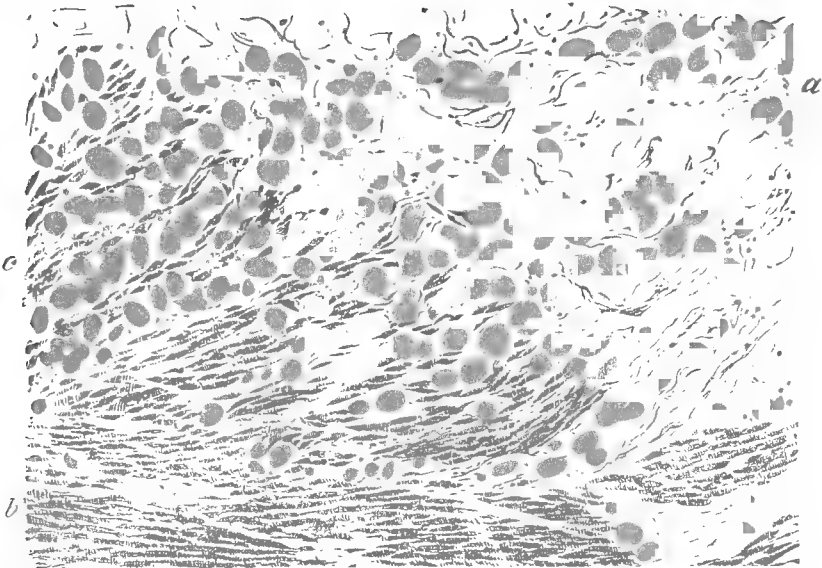
FIG. 45.—Adipose tissue from the panniculus of the heart. (Formalin, hæmatoxylin, and Sudan III.) *a*, Fat tissue; *b*, muscle; *c*, muscle infiltrated with fat tissue. × 40.

is reduced by the fat, causes the fat-drops to become blackened Fig. 48, *c*).

The fat contained in the special adipose tissues of the body is **stored fat** which the organism, in case of necessity, may use for its preservation, and it may be designated **fat for consumption** or **temporary fat**. Its abundance may be regarded as an indication of the condition of nutrition; when this is good the adipose tissues are well developed, in starvation and marasmus they may vanish entirely. There occurs **atrophy of fat-tissue,** in which the fat-cells contain only small droplets or no fat at all, in the latter case reverting to the type of ordinary connective-tissue cells. The atrophic fat-lobules often take on a pale yellow color through the formation of pigment in the cells (*yellow atrophy of adipose-tissue*). Through the collection of fluid between the atrophic fat-cells the fat-tissue (most frequently in the cardiac panniculus) becomes translucent, resembling myxomatous tissue (*serous atrophy of adipose tissue*).

Hyperplasia of adipose tissue leads to the condition known as **obesity, adipositas,** or **lipomatosis.** It is dependent primarily on excessive food-supply; but there are frequent exceptions to this rule, since

in many people an increased formation of panniculus does not take place, no matter how rich the food-supply. Again, an abundant deposit of fat occurs in some individuals when the food-supply does not exceed the
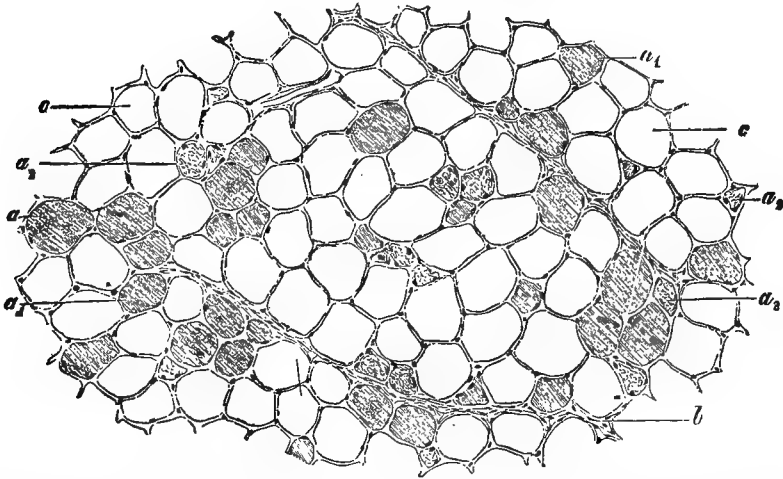
FIG. 46.—Lipomatosis of the calf muscles, associated with atrophy. (Müller's fluid, carmine.) *a*, Transverse section of normal fibre; *a₁*, of atrophic fibre; *a₂*, transverse section of sarcolemma tube containing disintegrated contractile substance; *b*, connective tissue; *c*, fat-tissue. × 60.

normal. In such cases the cause of the lipomatosis must be sought in inability on the part of the organism to destroy the fat brought to or arising in it.
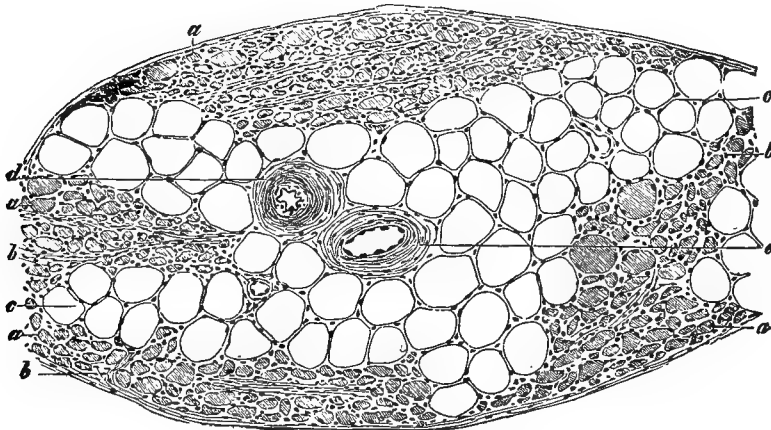
FIG. 47.—Spinal muscular atrophy with lipomatosis, in ascending atrophy of the anterior horns of the spinal cord. (Müller's fluid, Bismarck brown.) Section from the calf muscle. *a*, Transverse section of atrophic muscle-fibres; *b*, perimysium; *c*, fat-tissue; *d*, artery; *e*, vein. × 60.

In *general lipomatosis* the deposit of fat takes place first in the normal fat-depots, and later in places that normally contain no fat, for example, in the connective tissue of the muscles, in the myocardium, and

beneath the endocardium. *Local lipomatosis* may occur in various regions of the body, for example, in an arm, the front of the neck, nape, etc., and leads to deformities of the affected regions resembling elephantiasis. When occurring in circumscribed masses or nodules the con-
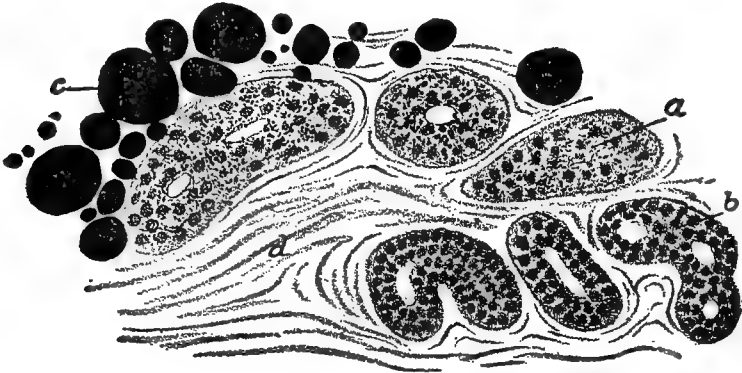
FIG. 48.—Skin with sweat glands, from the sole of the foot. (Osmic acid.) *a*, Thick gland coils with fine fat droplets; *b*, slender gland coils without fat droplets; *c*, fat drops lying about the gland coils. × 390.

dition is classed with the fatty tumors known as *lipomata* (see Lipoma). Local lipomatosis occurs as a disease of muscles, particularly those of the calves of the legs (pseudo-hypertrophic muscular paralysis) (Fig. 46, *c*) through the development of adipose tissue in the perimysium
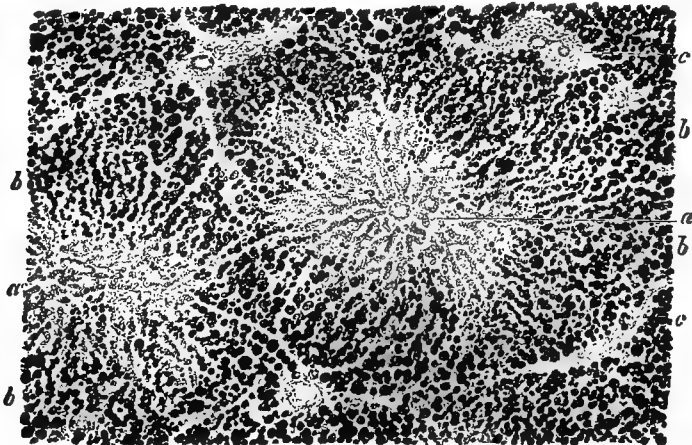
FIG. 49.—Fatty liver from a case of pulmonary tuberculosis. (Flemming's solution, safranin.) *a*, Central portion of the liver-lobule; *b*, peripheral zone containing fat; *c*, periportal connective tissue. × 30.

internum. At the same time they become weaker, since many of the muscle-fibres (Fig. 46, *a*, *a₁*, *a₂*) disappear. Finally, in other cases adipose tissue may develop secondarily in places where other tissue has disappeared, for example, in muscles (Fig. 47, *c*) that have become

atrophic as the result of disease of the anterior horn of the spinal cord or in lymph-nodes that in old age have lost the greater part of their lymphocytes.

The **fat of the glandular organs** occurs ordinarily in small, even minute droplets, but in the case of great abundance of fat larger droplets may be formed. The sebaceous, Meibomian, and lachrymal glands, and adrenals are normally rich in fat. It occurs to a lesser extent in the testicles and ovaries; still less in the salivary glands, thyroid and sweat glands (Fig. 48, *a*). The kidneys have the least fat-content of any of the glands. During the period of functional activity (testicles and ovaries) and in advanced age the fat-content is, in general, somewhat increased. The fat-content of glands is but slightly dependent on the general nutrition, so that it does not disappear during starvation (Traina). This glandular fat may be designated **permanent** or **intrinsic fat.**

The liver holds a special position among the glands so far as fat is

Fig. 50.—Fat-granule cells in an anæmic area of softening in the brain. (Marchi's fluid.) *a*, Fat-granule cells; *b*, blood-vessels. × 280.

concerned. As do other glands it contains a certain number of fine fat-droplets which do not disappear during starvation. In addition there also occurs a temporary storage of fat which, beginning in the periphery of the lobule, extends toward the centre (Fig. 49, *b*); and, finally, the liver may become completely changed into cells containing fat, and the parenchyma acquires a straw-color.

Fatty infiltration of the liver may result from excessive food-supply, but is more frequently observed in marasmic individuals, particularly in consumptives whose panniculus is atrophic. Inability on the part of the liver to destroy or to give off again the fat brought to it from the intestine or from the fat-depots appears to be the cause of this phenomenon.

Muscle-fibres, surface epithelium, the epithelium of different gland-ducts, connective-tissue cells, vascular endothelium, leucocytes, etc., show a *variable content of fat;* but without changes that can be regarded as degenerative in nature. In individual cases it is evident that the fat-content is dependent on an abundant supply from the intestine or transportation from the fat-depots, especially in those cases in which the leucocytes or the vascular endothelium (particularly that in the liver) are rich in fat. In other cases there are functional states during which a rich supply of fat appears (muscles).

All **animal** fats are mixtures of olein, palmitin and stearin, that is, combinations of oleic acid ($C_{18}H_{34}O_2$), stearic acid ($C_{18}H_{36}O_2$) and palmitic acid

($C_{16}H_{32}O_2$) with the trivalent alcohol glycerin ($C_3H_5[OH]_3$) to form neutral esters, the so-called triglycerides. Whether taken in as free fatty acids, as neutral fats, or as soaps, the process of absorption is always the same; they appear constantly in the form of neutral fats in the channels through which absorption takes place.

In close relationship to the body-fats stand the *lecithins* (combinations of each single molecule of glycerin-phosphoric acid with two molecules of fatty acid and the complex of an ammonium base, cholin), the *protagons*, and the *cholesterins*, substances which occur in small amount in various tissues, but abundantly in the myelin of the brain and peripheral nerves. Cholesterin occurs also in the bile.

The fat contained in the human organism is derived primarily from the **food-fat** taken up in the intestine. In the early weeks of life, when the intestine of the nursing infant is still abnormally permeable, the finest fat-droplets are taken up as such and carried through the lymph-stream into the blood. In later life the taking up of unchanged fat through the intestinal epithelium probably occurs to a slight degree or not at all, that is, the fat is, for the greater part, split up in the intestinal canal, and through the combination of the fatty acids with the alkali present in the intestine there are formed soaps soluble in water, which are absorbed by the epithelium. Even in the intestinal epithelium these soaps are changed into spherules of neutral fat (just as absorbed peptone is again changed into albuminate). The glycerin necessary for this change is absorbed directly from the intestine, where it is present in a free state arising from the splitting of the neutral fats.

In the entrance of the fat into the cells of the fat-depots the fat-molecule is again split up and then reconstructed in the cells.

According to *Arnold*, the entrance of fat into the cells is associated in many cases with a certain activity of the plasmosomes, and is therefore connected with the cell-granules, which he regards as the morphological products of the function of the plasmosomes. In intracellular fat-formation, designated by him as **granular fat-synthesis**, which occurs in leucocytes and lymphocytes, also in endothelial, connective-tissue, cartilage, epithelial and gland cells, soap is taken into the cells in soluble form and undergoes granular change into fat. The fat-droplets appear at the site of the antecedent granules.

In this manner there arise in part the so-called **fat-granule cells**, leucocytes and lymphocytes closely packed with fat-droplets, that occur in areas of necrosis and inflammation, particularly in the central nervous system (Fig. 50, *a*). According to *Arnold* the uniform size of the fat-droplets speaks in favor of such an origin. Such granule-cells may also be formed through *phagocytosis;* that is, the amoeboid cells may take up through their protoplasmic movements fat-droplets lying free in the tissues (in softening of the brain and spinal cord they arise through disintegration of the medullary sheaths). In the event of such occurrence, chemical and morphological changes in the material taken up are not excluded.

The **carbohydrates** form a second source of fat-formation in the organism, but the chemical processes attending the formation of fat from carbohydrates have not been determined. It is probable that the amount of fat so formed is relatively much less than the fat taken in as such from the food. It is still a question as to whether fat can be formed in the body from **albumin**. Since many facts speak for the transformation in the animal body of certain groups of the albumin-molecule into glycogen or grape-sugar, the theoretical possibility of the formation of fat from albumin cannot be denied (*Kraus*).

Of the fats and lecithins present in the organism, those containing oleic acid alone reduce osmium tetraoxide to a black osmium hydroxide, so that treatment with osmic acid or Flemming's solution does not show the presence of palmitin and stearin. On the other hand, Sudan III and Scharlach-roth (ponceau) stain all the fats.

§ 56. **Fatty degeneration** or *fat-metamorphosis* is *that condition* of *the cells* in *which fat-droplets appear* in *the protoplasm* in *such manner as to indicate a change in the chemico-physical cell-structure.* In a part of the cases this change may be inferred from the appearance of the cells, in that fragmentation, distintegration (Fig. 51, *e, f*), and separation of the cells from their substratum may be demonstrated.

The views of Virchow were formerly accepted, that in lipomatosis there occurred a deposit of fat from the blood and tissue-juices; while

fatty degeneration represented the formation of fat from the albumin of degenerating cells. Recent investigations make the latter view doubtful. Although the possibility of formation of fat from albumin cannot be denied, it has not yet been proved that this is the case in the so-called fatty degeneration of cells.

In many cases what we call fatty degeneration is the expression of a *molecular physical rearrangement* of the cells, a fat-metamorphosis, in which the fat contained in the cells in a form that cannot be recognized microscopically is separated out in the form of visible droplets. Therefore, an increase in the actual fat-content of the cell does not occur in fatty degeneration. Renal cells that on microscopical examination show no fat may, nevertheless, contain twenty per cent of fat. Should degeneration occur, so that the fat becomes visible in

FIG. 51.—Fat-containing liver-cells. *a* and *b*, Fat-infiltration; *c, d, e, f,* fatty degeneration. × 400.

FIG. 52.—Fatty degeneration of the heart-muscle. × 350.

the form of droplets, the total fat-content is not increased (Rosenfeld, Kraus). A process similar to that taking place in the body occurs during the autolysis of tissue preserved aseptically in the incubator, fat-droplets
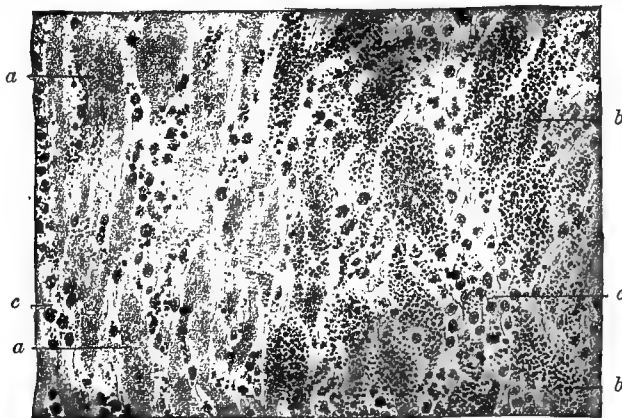
FIG. 53.—Anæmic and fatty necrosis of the myocardium 85 hours after the closure of a coronary artery. (Flemming's solution, safranin.) *a*, Necrotic; *b*, fatty muscle fibres; *c*, connective tissue with leucocytes containing fat. × 300.

becoming visible in such tissues (Hansen, Wentscher, Kraus, Müller, and others). When fat as such is not present in the cells it may arise through chemical decomposition of *lecithin, cerebrin,* and *protagons* (myelin) contained in the cells.

A second source of fat appearing in fatty degeneration is the *fat brought to the affected cells by the blood and tissue-juices,* arising either from the fat contained in the food or transported from the fat-depots in other tissues. For example, in phosphorus-poisoning transportation of fat from the panniculus to the liver takes place. It is probable that

the same thing occurs in other intoxications (arsenic, alcohol, chloroform, oleum pulegii). In such cases increase in the fat-content of the affected organ must occur, but this is not always the result of synthesis of fat, that is, the formation of higher fatty acids and glycerin and their combination, but is a taking-up of fat that, either as such or as soaps, has been given over to the blood.
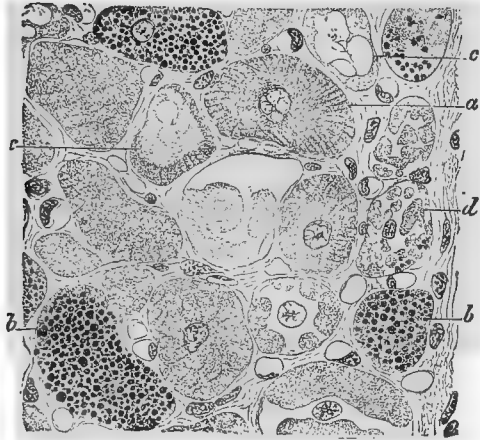
FIG. 54.—Fatty degeneration, vacuolization, and disorganization of the heart-muscle in a patient dying from pneumonia and nephritis. (Flemming's, safranin.) a, Transverse section of normal muscle-cell; b, muscle-cell in a state of fatty degeneration; muscle-cells with vacuoles; d, disorganized cell. × 400.

In the condition which we call fatty degeneration, the fat appears usually in the form of fine droplets (Figs. 52, 53, b, 54, b, and 55, b), but these may become confluent to form larger drops (Fig. 56), particularly during the disintegration of the cell (Fig. 51, f). The conditions under which the fat of fatty degeneration appears make it probable that the *cells which are the seat of fatty metamorphosis are still living, but have been injured by external influences.* In anæmic infarcts of the spleen, kidneys, and heart, the fatty cells (Fig. 53, b) are found in the zone of transition between the necrotic (a) and the living tissue; that is, where the circulation of the blood and lymph is weak, but has not ceased. The appearance of fatty cells in glands (Fig. 51, c, d, e, f), in the endothelium of the blood-vessels, or the cells of the heart-muscle (Fig. 54, b) occurs in intoxications and infections as the result of cell-injury through toxic action. Chronic fatty degeneration of the heart-muscle (Fig. 55, b) is seen in valvular lesions, pulmonary emphysema, general anæmia; in the renal epithelium of consumptives it occurs partly as the result of diminished supply of oxygen, and partly from

FIG. 55.—Marked fatty degeneration (chronic) of the heart-muscle. (Flemming's solution, safranin.) a, Normal muscle; b, muscle which has undergone fatty degeneration. × 80.

the action of toxic substances. Experimental investigations have shown that long-continued elevation of the body

temperature leads to fatty degeneration of different tissues (heart, kidneys, and liver).

A mild grade of fatty degeneration cannot be seen with the naked eye. The more severe forms give an opaque yellowish color to colorless tissues, as, for example, the intima of blood-vessels and the heart-valves, which frequently show patches of fatty metamorphosis. The cortex of a kidney in a state of fatty degeneration becomes grayish or yellowish. In the heart-muscle the yellowish discoloration of fatty degeneration, particularly when the change is localized in small foci (Fig. 55, *b*),
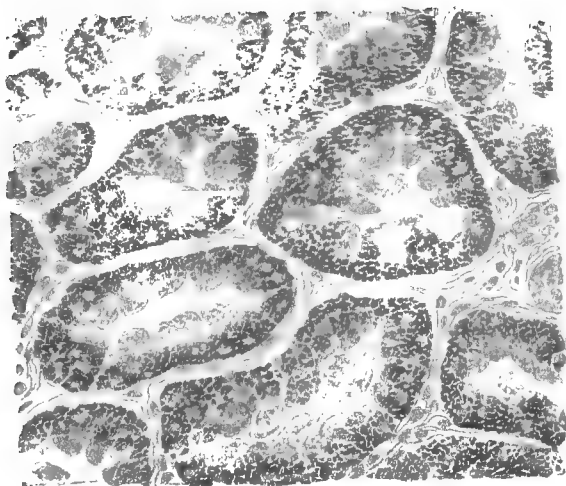
FIG. 56.—Fatty degeneration of the renal epithelium, from a case of chronic pulmonary tuberculosis. (Formalin, hæmatoxylin, Sudan III.) × 300.

stands out prominently ("tiger-heart"). The change is best seen immediately beneath the endocardium covering the papillary muscles of the left ventricle.

It is not always possible to decide whether the fat present corresponds to a physiological or pathological condition. We can no longer accept the view that fine droplets of fat in the cells signify a pathological condition, since most glands and other tissues, for example, muscle-fibres, contain fat-droplets under normal conditions.

In **fat transportation** the fat may appear in the blood in the form of large or small droplets (lipæmia). This is most marked in traumatic lesions of adipose tissue leading to fat-embolism. Large fat-drops that remain in the vessels disappear slowly. Proliferation of the vessel-wall may occur at the site of the embolism, not only after the direct introduction of fat into the blood-vessels, but also after feeding with fat, as in the administration of cod-liver oil (*Wuttig*).

If fasting dogs are fed with mutton-tallow, there is a deposit of mutton-tallow in the fat depots. If they are then poisoned with phosphorus, oleum pulegii, or phloridzin, their livers, which show fatty degeneration as the result of the poisoning, are found to contain mutton-fat in addition to the animal's own fat (*Rosenfeld*). According to *Leick* and *Winckler,* the mutton-fat under these conditions is also found in the heart-muscle. In dogs fed with iodopin and afterward poisoned with phosphorus, the iodized fat passes into the liver. In animals devoid of adipose tissue no fatty degeneration occurs in the liver after poisoning with phosphorus or phloridzin (*Rosenfeld, Fibiger*).

In the case of *aseptic autolysis of the liver* outside the body *Waldvogel* has made chemical and histological investigations which seem to show that fat and fat-like

products of disintegration may arise *in loco;* and there occurs an increase in those bodies which, related to albumin, have a fat-like (jecorin, lecithin, protagon) or fatty character (fat-acids, neutral fat). In phosphorus-poisoning (*Waldvogel* and *Tintemann*) protagon and jecorin appear as disintegration-products of albumin (the lecithin present is for the greater part transformed into substances which after acetone precipitation make up the residue of the substances soluble in ether). Similar disintegration of the albumin-molecule occurs in autolysis.

According to *Dietrich,* fat does not occur in the process of autolysis.

In certain degenerating cells doubly refractive droplets similar to fat are found, but they stain only slightly with osmic acid (adrenals, corpus luteum, etc.). They are regarded by various authors (Albrecht, Kaiserling, Orgler, etc.) as *myelin,* similar in character to the myelin of nerve-fibres. It is also probable that protagon appears in this form. Such droplets may be found in the autolysis of cellular tissues.

The kidneys may contain less fat than normal and yet show much fat both to the naked eye and on microscopical examination, as the
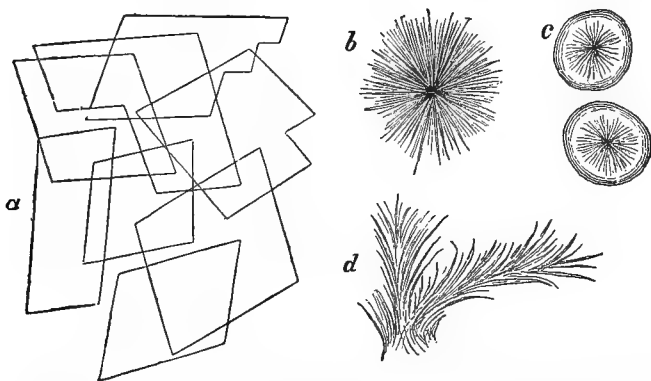
FIG. 57.—*a,* Cholesterin plates; *b,* free cluster of margarin needles; *c,* needles enclosed within fat-cells; *d,* grass-like bunch of margarin needles. × 300.

result of liberation of the fixed fat in fatty degeneration. The invisible fat is set free and becomes visible. The condition of fatty degeneration may be defined, therefore, as an *infiltration of fat from outside into cells degenerating under the influence of poisons or other injurious agents (liver, heart-muscle, pancreas) or as a setting free of the invisible intracellular fat through autolysis (kidneys, spleen, muscle).*

§ 57. The **fats** in the human body consist almost entirely of a mixture of the glycerin-esters of oleic, palmitic, and stearic acids which are designated *olein, palmitin,* and *stearin.* The first is fluid at ordinary temperatures, the second melts at 46°, the third at 53° C. Since the body-fats contain varying proportions of olein, palmitin, and stearin, they vary in consistence and melting point. If after death the tissues of the body are cooled below the melting-point of the contained fat, the stearin and palmitin separate and form stellate or feathery needles (Fig. 57, *b, c, d*), which are commonly called **margarin needles,** and are found sometimes in fat-cells, at other times free.

Cholesterin occurs in the form of delicate rhombic plates (Fig. 57, *a*), the edges and corners of which are often notched. These crystals may be found wherever there are masses of detritus containing fat, aris-

ing from degenerating cells or extravasations of blood, as in collections of fluid in the tunica vaginalis testis, in dilated sebaceous glands, or in softened areas in the wall of diseased vessels (aorta, iliacs, etc.). When the substance in which the cholesterin plates are formed is fluid, they may be visible to the naked eye as glistening scales.

Cholesterin $(C_{27}H_{44}O)$ is a constituent of bile, and is furnished by the mucous membrane of the gall-bladder and bile-ducts, and held in solution by the bile salts and soaps. It is also found in the medulla of nerve-fibres, and in small amounts in the blood, where it is held in solution by fats and soaps. According to Burchard traces of cholesterin are found in all the organs.

Cholesterin is insoluble in water, dilute acids, caustic alkalies, and cold alcohol; it is soluble in boiling alcohol, ether, choloroform, and benzol.

When treated with a mixture of five parts of concentrated sulphuric acid and one part of water the edges of cholesterin crystals take on a carmine-red color, which gradually passes into violet. Sulphuric acid and water in the proportions of three to one give a violet color to the edges of the crystals. Concentrated sulphuric acid containing a trace of iodine colors the crystals violet, blue, green, and red.

The origin of cholesterin is not known. It is probable that it is an intermediate product in the decomposition of albumin, since it is found in those pathological conditions in which albuminous substances are in process of disintegration.

Literature.

(*Cholesterin.*)

Rosenbloom: Arch. Int. Med., 1913, 12, 395.

VII. The Deposit of Glycogen.

§ 58. **Glycogen** $(C_6H_{10}O_5)^n$ is a carbohydrate which is readily convertible into sugar; and in the body is formed chiefly from the carbohydrates of the food.

In the tissues of the body, glycogen is found as a *hyaline substance,* most often in the cells, but occasionally in the tissue-spaces. It usually occurs in the form of spherules or lumps of different sizes. In the cells these spherules are most frequently found in the neighborhood of the nucleus.

Glycogen is soluble in water, but the solubility of that found in different tissues varies (Langhans); that found in the liver, kidneys, muscles, and pus-corpusles is more easily soluble than that of cartilage-cells and surface epithelium. Fixation of the tissue in alcohol renders the glycogen less soluble in water. After death the glycogen of the liver is quickly converted into sugar through the action of a diastatic ferment.

Glycogen becomes brownish-red when treated with iodine. By the method of Best, glycogen is stained red with carmine (Fig. 58, *b, c*).

Glycogen is present in almost all the tissues of the embryo, in the fœtal membranes at an early period of development; and in the adult body in the liver-cells, muscles, heart, cartilage, in the epithelium of various organs, in the leucocytes, and in the blood-serum (Gabritschew-

ski). During starvation the glycogen of the liver is diminished, and in other pathological conditions may disappear.

Glycogen appears in increased amount, particularly in diabetes, in the blood and kidneys. The epithelium of the renal tubules contains numbers of small drops (Fig. 58, *b*), and large drops (*c*). Since this deposit leads to destruction of cells, the condition may be designated glycogen degeneration.

Glycogen also occurs in inflammatory foci (Gierke), usually in the polynuclear leucocytes, but also in the so-called epithelioid cells, fibro-
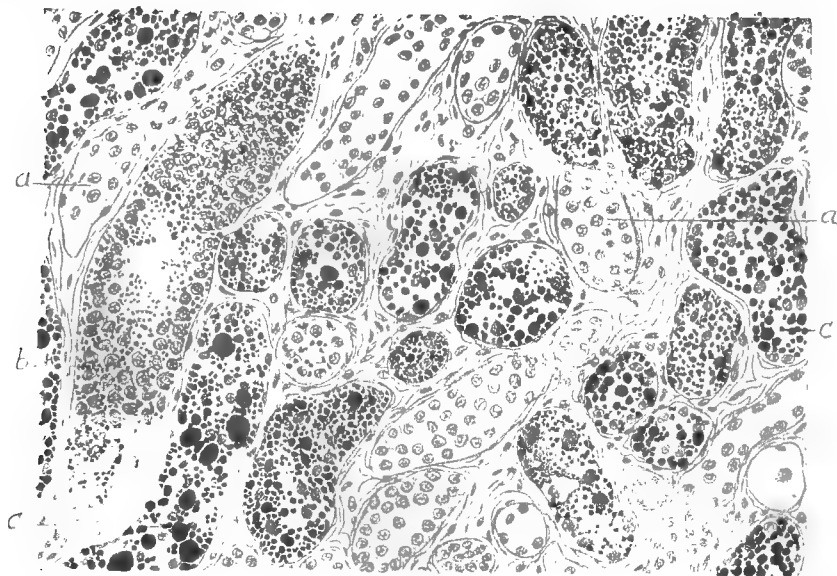
Fig. 58.—Glycogen degeneration of the renal epithelium in a case of diabetes. (Compare Gierke, l. c.) *a*, Normal tubules; *b*, epithelium with early stage of glycogen deposit; *c*, advanced glycogen deposit with epithelial destruction. × 300.

blasts, and the giant-cells developing from these, and in the tissue bordering on the inflammatory area. Glycogen is also found in many tumors, carcinomata and sarcomata.

It is difficult to determine the **significance of the glycogen appearing in pathological conditions.** Since glycogen is abundant in embryonal tissues and in quickly growing tumors, *Brault* is of the opinion that its appearance is a sign of increased proliferative cell activity; but the presence of glycogen in large amounts in pus-cells does not agree with this theory. Moreover, in tumors it is not found in the regions of most active cell proliferation. According to *Gierke,* glycogen appears by preference in those tissues deprived of circulation. A certain parallel exists between the occurrence of fatty degeneration and glycogen deposit. Both changes are found, for example, in inflammatory foci and at the edge of necrotic areas. In both cases degenerating cells are present that are able to take up both fat and glycogen, but can no longer change them.

According to *Wolff,* the leucocytes in normal blood contain glycogen, but this glycogen is easily soluble, and therefore difficult to demonstrate. In many inflammatory exudates the glycogen of the leucocytes becomes less soluble and can be more easily demonstrated.

The iodophile hyaline substance contained in the tissues is not a pure glycogen, but is most probably a combination of glycogen with an albumin-like substance.

To avoid the solution in water of glycogen in fresh preparations, a syrupy solution of iodine in gum (*Ehrlich*) or iodine-glycerin (*Barfurth*) may be used. Sections of tissues hardened in alcohol are treated (*Langhans*) with a dilute tincture of iodine (1 part tincture iodine to 4 parts absolute alcohol), and cleared in oleum origani in which the reaction is preserved for a long time. The reaction is also preserved in hard Canada balsam. For the staining of glycogen with carmine, *Best* gives the following method: the sections are first stained with hæmatoxylin and then for three-fourths to one hour in a mixture of two parts of a solution of carmine (carmine 1.0 grm., ammonium chlorate 2.0 grms., lithium carbonate 0.5 grm., aq. dest. 50 grms., brought to a boiling-point, after which there is added 20 c.c. of liq. ammon. caust.), 3 parts of liq. am. caust. and 6 parts of methyl alcohol. They are decolorized for a few minutes in a mixture of 2 parts methyl alcohol, 4 parts absolute alcohol, and 5 parts water, and mounted in Canada balsam.

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VIII. Mucous Degeneration.

§ 59. **Mucous degeneration** has its physiological prototype in the production of mucus by the mucous membranes and mucous glands, and in the formation of mucus in the connective tissue of the umbilical cord, tendons, bursæ, and synovial membranes. In the umbilical cord the mucus occurs as a jelly-like matrix; in the joints, bursæ, and tendon-sheaths it forms a clear, stringy fluid.

In the epithelium of the mucous membranes the mucus appears first in the goblet-cells (Fig. 59, *a*), forming a clear substance which stains with hæmatoxylin. In mucous glands, during the process of mucus formation, the epithelial cells swell, their central portions become clear, and the granules of the protoplasm are reduced to small groups or strands. The so-called mucous corpuscles of the salivary secretion, which are characterized by glassy, transparent contents and vibrating protoplasmic granules, are round cells which have undergone mucous degeneration.

The mucus formed from the protoplasm of the cells may be discharged, and the cells remain intact, or they may be destroyed.

Mucus is produced in the same way under pathological conditions as under normal (Fig. 59, *a*). In catarrh of the mucous membranes there is increased formation of mucus by the cells of the superficial epithelium as well as those of the glands. In mucous membranes covered with

cylindrical cells the number of goblet-cells is increased, and in the secretion there are found cells which have undergone complete mucous degeneration — that is, they have been converted into glassy masses enclosing few granules. Other cells contain mucus in the form of drops of varying size.

The epithelium of diseased tissues may also undergo mucous degeneration, in a manner similar to that occurring in normal tissues. Thus the epithelial lining of cysts of the ovary and of intestinal tumors may often contain numerous goblet-cells (Fig. 60, a), and cells which have undergone total mucous degeneration (b). In the so-called gelatinous or mucoid carcinoma (colloid carcinoma) a large part of the epithelial cells suffers mucous metamorphosis.

Of the *connective tissues,* which may suffer mucous degeneration and acquire a gelatinous, transparent appearance, may be mentioned fibrous connective tissue, cartilage, bone, adipose tissue, bone-marrow. In these tissues it is chiefly the ground-substance (Fig. 61, b) which undergoes mucous change and is converted into a homogeneous, structureless mass. The cells themselves may remain unchanged, or may become fatty, or even undergo mucous degeneration. In the last event the entire tissue ultimately forms a hyaline mass, in which only scattered fibres of connective tissue, or single cells or groups of cells are left to suggest the original tissue.

FIG. 59. — Formation of mucus within the epithelial cells of an adenomatous polyp of the small intestine. (Alcohol, hæmatoxylin.) a, Epithelium with dark-stained (hæmatoxylin) drops of mucus within the cells; b, free mucus; c, leucocytes in the epithelium. × 300.

The stringy, or gelatinous material, which results from mucous degeneration, does not represent a single chemical substance; in it there

FIG. 60.
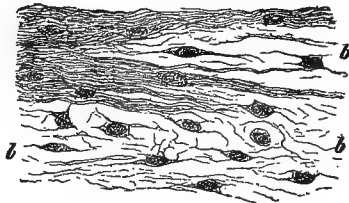
FIG. 61.

FIG. 60.—Epithelial cells which have undergone mucous degeneration, from a cystadenoma of the ovary. a, Cells showing slight change; b, cells showing marked degree of mucous change. × 400.

FIG. 61.—Mucous degeneration of the connective tissue of the aortic valves (osmic acid, glycerin). a, Fibrous tissue; b, myxomatous tissue. × 350.

may be found different varieties of mucins as well as of pseudomucins.

The **mucins** (submaxillary, intestinal, and tendon mucin) are nitrogenous substances resembling albumin. They dissolve or swell in water forming a mucoid fluid, from which they may be precipitated in

a stringy form by means of alcohol or acetic acid; but differ from the true albumins in the fact that the precipitate is not redissolved in an excess of the acid. The precipitated mucins are soluble in neutral salt-solutions, caustic alkalies, and alkaline carbonates; and are gradually converted into alkali-albuminates in case of solution by the last named.

All mucins contain nitrogen and sulphur; their content in carbon, oxygen, nitrogen, and sulphur varies in the different forms.

Pseudomucin also dissolves in water, forming a gelatinous fluid, from which it may be precipitated in stringy masses by alcohol. The precipitate redissolves in water. Solutions of pseudomucin are not precipitated by acetic acid.

Pseudomucin is found particularly in ovarian cystomata, and is the cause of the gelatinous character of the cyst-contents. It is produced by the epithelium of these tumors (Fig. 60); and in its formation the same changes take place in the cells, as in the formation of mucin from epithelium. In all probability the mucous substance present in gelatinous carcinomata is a body closely related to pseudomucin or metalbumin — that is, there are different varieties of pseudomucin (Pfannenstiel), of which the two mentioned àre examples.

IX. Formation of Epithelial Colloid and Epithelial Hyaline Concretions.

§ 60. The **epithelial formation** of **colloid** is a process closely related to the epithelial production of mucus; it consists partly in secretion of colloid by gland-cells, and partly in conversion of cells into colloid.
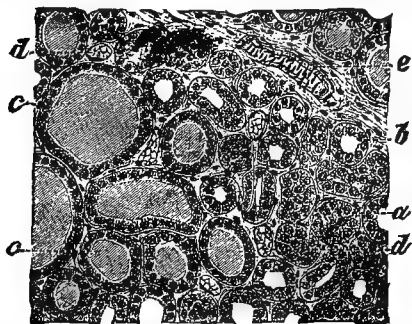
FIG. 62. FIG. 63.

FIG. 62.—Colloid in enlarged thyroid gland. (Alcohol, hæmatoxylin.) *a*, Follicle filled with cells; *b*, follicle showing lumen; *c*, masses of colloid; *d*, capillary; *e*, connective-tissue septum with artery. × 60.
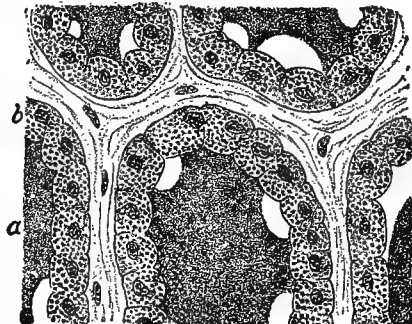
FIG. 63.—Secretion of colloid in the thyroid. (After Bozzi.) *a*, Colloid; *b*, secreting cells with granules.

Physiologically, colloid is found in the thyroid (Fig. 63), where it appears in the form of *hyaline, rather firm, colorless, or faintly brownish, jelly-like masses,* which fill the vesicles, but from these may extend into the lymph-vessels of the thyroid. *Pathological collections of colloid* occur both in residual thyroid tissue and in newly-formed glandular-tissue of pathological nature. The accumulation causes a more or less marked distention of the vesicles, and leads to enlargement of the gland, known as colloid goitre.

The secretion of colloid is characterized by the formation of homogeneous granules and spherules in that portion of the epithelial cells next to the lumen of the vesicle (Fig. 63). Some of the cells may be completely filled with these granules. In excessive and atypical formation desquamated cells may become converted into hyaline colloid.

The colloid of the thyroid is found on microscopical examination to be *homogeneous;* and because of its physical properties it may be designated **epithelial hyalin.** As a rule it incloses no cellular elements, although degenerating cells may be found in it. Alcohol and acetic acid cause no clouding, or precipitation in the form of
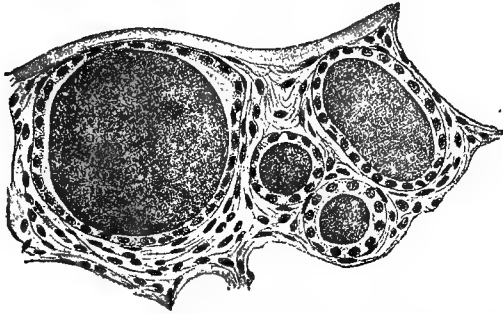
FIG. 64.—Dilated urinary tubules filled with colloid. (Müller's fluid, hæmatoxylin, and eosin.) × 250.

threads, as happens in the case of mucin when so treated. By Van Gieson's method colloid is stained orange-red, while the connective tissue takes a fuchsin-red. It must be noted that the contents of the thyroid follicles, which are designated colloid, are not always of the same character. At one time the substance is firm, at another soft or even fluid, or at least is readily soluble in water. In preparations fixed in alcohol granulation or cleavage may be caused by contraction; moreover, the staining reactions are not always the same.

The chemical nature of the thyroid colloid is not fully known, and it is probable that the contents of the follicles are of variable composition. It is most probably an albuminoid body which is combined with iodothyrin, the active principle of the thyroid gland.

Epithelial hyalin is also found in the

FIG. 65.—Colloid concretions in the cystic dilated tubules of the parovarium. (Formalin, Van Gieson's stain.) *a, b,* Glandtubules of the parovarium; *c,* cysts containing colloid concretions (*d*). × 80.

glandular elements of the hypophysis cerebri, in the tubules of diseased kidneys (Fig. 64), in the prostate (Fig. 66, *d*), in cysts of the parovarium (Fig. 65, *d*), in the glands of the stomach, and more rarely in other glands. In the last-named organs the hyalin occurs in the form of a uniformly homogeneous mass completely filling the gland-lumen, or as

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hyaline, in part **laminated concretions** (Fig. 65, *d,* and 66, *d*) of more or less firm consistence.

It must not be assumed that the last-named formations are identical in their chemical composition with thyroid colloid. The only thing which they possess in common is this: they both represent *transformed protoplasm of gland-cells* — a substance which is *hyaline,* possesses a certain firmness, and *does not react to chemical reagents in the same manner as does mucin.* These concretions may also undergo changes which necessitate, on their part, a different behavior toward microchemical reactions. This is particularly true of the prostatic concre-
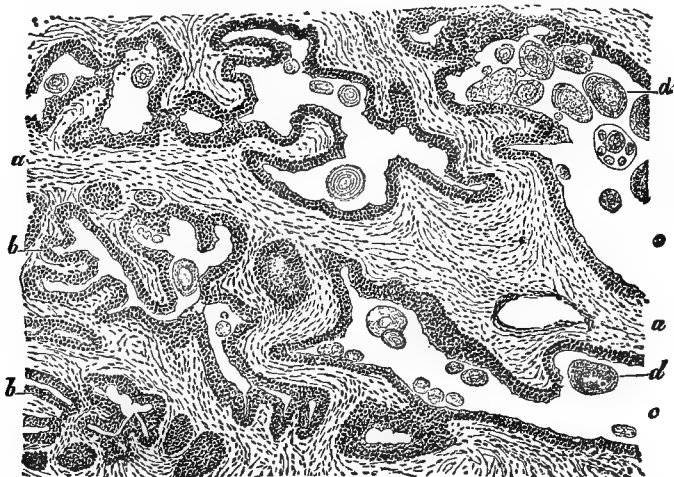
Fig. 66.—Section from a hypertrophic prostate with concretions. (Müller's fluid, hæmatoxylin, and eosin.) *a,* Stroma; *b,* glands; *c,* dilated glands; *d,* concretions. × 45.

tions, which not infrequently show, when treated with iodine, a reaction that has been taken as evidence that they are composed of amyloid material (see § 63). It may be proved, both in the case of prostatic concretions and of renal colloid, that they represent cell-material which has become changed into hyaline substance. In the case of renal colloid, however, it is only under special conditions that the participation in its formation of albumin derived from the glomeruli may be excluded.

Colloid is a collective term which is applied to a variety of formations that possess certain physical attributes in common. There is great difference of opinion among authors as to the application of the term. Under colloid degeneration, for example, *von Recklinghausen* places mucous, amyloid, and hyaline degenerations; including under the last-named epithelial colloid-formation, hyaline degeneration of connective tissue, as well as hyaline coagulation-necroses and hyaline thrombi. *Marchand* gives the term a more limited application, but includes under colloid certain forms of epithelial mucin-formation (particularly in tumors), and also hyaline formations in connective tissue. Inasmuch as colloid is not a chemical entity, and as its staining-reactions do not differentiate it from other hyaline substances, *Ziegler* thought it expedient to apply the term only to those hyaline products of epithelium which do not possess the characteristics of mucin. He, therefore, also classified as colloid those epithelial concretions which on account of their reaction with iodine (brown or blue color when treated with dilute iodine solutions) have hitherto been regarded as amyloid bodies If objection is made to the classification of these formations as colloid, they may be placed under the

heading of **epithelial hyalin.** (*Ziegler's* application of the term colloid has been respected in the present revision.)

Hyaline spherules have been described by Russell and others, particularly in cancer cells, and, at one time, were regarded in certain quarters, as etiologically related to cancer. It is now generally believed that these so-called "fuchsin bodies" represent phagocytised and hyalinised red blood cells. They occur in a wide variety of conditions and are noticably frequent in the mucosa of the stomach in pernicious anemia.

In certain infections, notably typhoid fever and influenza, the lower end of the rectus muscles not infrequently shows changes characterized by hyalinization, the areas appearing smooth, opaque and grayish pink in color. On microscopic examination, it is found that the muscle fibres are swollen, opaque and glassy (*Zenker's degeneration*.) In the recently prevailing pandemic of influenza, this variety of degeneration was encountered in the rectus muscles in a considerable proportion of all cases examined at autopsy. Rupture of the hyalinized muscle fibres occasionally occurred with the production of extensive hæmorrhage into the sheath and mechanical disintegration of the remaining muscle fibres. In still other cases, hyaline degeneration and hæmorrhage were followed by secondary infection and abscess formation.

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X.   The Pathological Cornification of Epithelium.

§ 61. **Cornification of surface epithelium** is a physiological process, characterized by the fact that the cells in the outer strata of the prickle layer of the *stratum germinativum* undergo horny change. This cornification takes place first at the periphery of the cells and in the bridge-like processes binding the cells together, at the same time the inner portions of the cell and the nucleus shrink, so that the cells become changed into scales. This horny substance or *keratin* is a modified albuminoid body of homogeneous composition, and is capable of resisting digestion by the gastric or pancreatic juices.

As accompaniments of cornification there appear in the cells of the prickle layer hyaline granules and spherules resembling colloid, which stain intensely with nuclear stains and are known as *keratohyalin*. In those areas of the skin possessing a thick horny layer, there is formed a stratum of keratohyalin-containing cells; this is known as the *stratum granulosum*. In those places where the horny layer is thin, the stratum granulosum is imperfectly developed and exhibits breaks of continuity.

Pathological cornification may occur as a wide-spread or localized increase of the horny layer, resulting in *hypertrophy of the epidermis* (see Chapter VI., § 76), or *hyperkeratosis*. This phenomenon may be primary — that is, due to causes inherent in the skin (ichthyosis, lichen pilaris) — or acquired as the result of external influences, mechanical lesions (callosities, corns), infections and inflammations. Further, there may occur disturbances in the process of cornification of the skin, so that certain pathological manifestations recognizable by the naked eye make their appearance, such as desquamation of the skin. Such changes are included under the term *parakeratoses*. They occur especially as sequelæ or concomitant phenomena of infections of the epidermis, and of inflammations of the corium and papillary body, sometimes without any recognizable cause; and in these cases either the process of cornification or of the formation of keratohyalin, or both, is disturbed.

Finally, *pathological cornification often occurs in regions where normally it either does not occur at all or but to a slight extent.* In the skin the cornification may extend to the ducts of the sebaceous glands and to the hair-follicles (ichthyosis) or to the sweat-glands (porokeratosis). Further, pathological cornification occurs not infrequently in the mucous membrane of the mouth, giving rise to white thickenings of the epithelium or to hair-like formations (hairy tongue). Horny change may be observed also in the mucous membrane of the middle ear, in the mastoid cells, in the descending urinary passages, and in these places it may lead to the formation of shining white scales (*formation of cholesteatomata*).

Cornification of cancer cells is very frequently seen, particularly in cancers of the skin, in which the horny scales are found usually in the form of round masses resembling onions or pearls. Similar horny products are also found in *cholesteatomata of the pia and brain.*

The pathological formation of horny substance in the mucous membranes or in tumors takes place either simply through cornification of the cell-membranes with contraction of the cell, or it may be combined with the formation of keratohyalin as in the case of typical cornification. The formation of keratohyalin and the cornification of epithelial cells often are irregularly distributed, particularly in cancers.

XI. Amyloid Degeneration and the Amyloid Concretions.

§ 62. **Amyloid degeneration** is characterized primarily by the deposit of an albuminoid substance (amyloid) in the connective tissues of blood vessels, so that the involved organ increases in bulk and acquires a glassy, homogeneous appearance. The degeneration may occur in almost all the organs of the body; but is especially frequent in the spleen, liver, kidneys, intestine, stomach, adrenals, pancreas, and lymph nodes. It is rarely observed in adipose tissue, thyroid gland, aorta, heart, muscles, ovaries, uterus, and urinary passages.

Extensive deposits of amyloid may be recognized by the naked eye, as the affected parts present a translucent appearance resembling bacon (*lardaceous degeneration*).

In the *spleen* the deposit of amyloid occurs first in the walls of the blood vessels of the lymphoid follicles, and the follicles finally are converted into homogeneous, translucent bodies (Fig. 67, *b*) resembling grains of boiled sago — this form of amyloid spleen is known as *sago spleen*. When the amyloid change occurs throughout the spleen-pulp it may be recognized on the cut surface as more or less distinct spots or streaks. Ultimately the greater part of the substance of the spleen may be replaced by amyloid material. The spleen is thus enlarged, its consistence becomes hard, and the organ may finally be transformed into a bacon-like substance (*lardaceous spleen*).

The *liver*, in well-marked amyloid degeneration, is increased in size and consistence. On section, the liver-tissue is found to be replaced to a greater or less extent by translucent, lardaceous masses, between which the remaining liver cells appear brownish or yellowish from abundance of contained fat.

The *kidney*, in cases of extensive amyloid change, is likewise enlarged and hardened, and on section shows hyaline, lardaceous spots and streaks of firm consistence. More often the kidney is normal in size or only slightly enlarged, but increased in consistence, while in the cortex the

presence of amyloid material is revealed by minute waxy, translucent spots corresponding to infiltrated glomeruli. In order to bring these out it may be necessary to treat the tissue with iodine. In still other instances the amyloid is apparent only on microscopic examination.

In the intestine and lymph nodes the degeneration usually cannot be recognized without the aid of the microscope and chemical reagents; and the same is true in regard to the other organs which are more rarely affected, such as adipose tissue, heart-muscle, the great blood-vessels, the thyroid gland, etc.

The substance which is deposited in amyloid degeneration forms
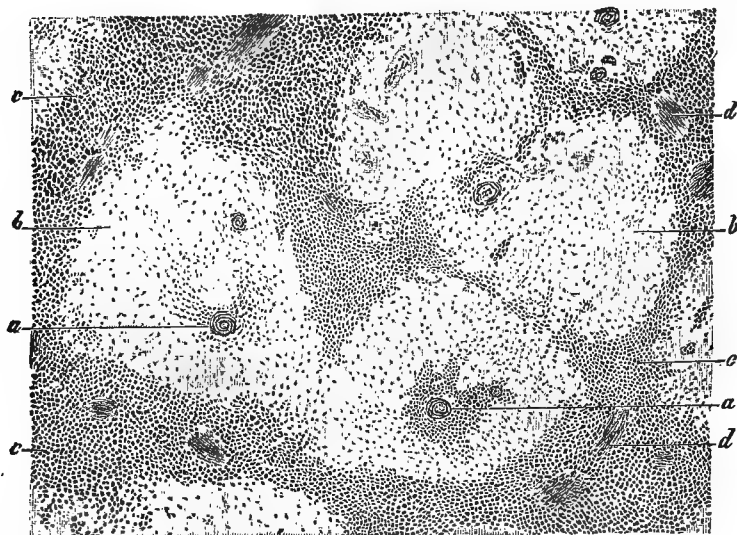
FIG. 67.—Amyloid degeneration of the splenic follicles and neighboring tissue. (Müller's fluid, hæmatoxylin, and eosin.) *a*, Transverse section of splenic artery; *b*, amyloid areas; *c*, pulp; *d*, trabeculæ. × 30.

shining, homogeneous masses, which exhibit a *characteristic reaction with iodine as well as with various aniline dyes. Iodine* dissolved in water, or better in a solution of potassium iodide, and poured over the affected tissue, stains the amyloid substance *dark brownish-red* (mahogany brown). In thin sections, under the microscope, the amyloid appears bright *brown-red* (Fig. 68, *b*) while the remaining tissue is a straw-yellow color.

In marked amyloid degeneration, when the tissues are of wooden hardness, the iodine reaction sometimes gives a *blue* or *green color.* Preparations which have been changed to mahogany brown through the action of iodine become still deeper brown when treated with dilute sulphuric acid or with a solution of zinc chloride, or they may become bright red, violet, blue, or green. This reaction is, however, imperfect in the majority of cases.

Methyl violet stains amyloid *ruby red* (Fig. 69, *a, b*), while the normal tissue takes a blue or dark blue-violet.

Because of the peculiar reaction with iodine, Virchow was led to regard the amyloid substance as a non-nitrogenous body related to cellu-

lose or starch, inasmuch as cellulose when treated with iodine and concentrated sulphuric acid becomes bright blue, and starch similarly treated gives an ultramarine color. Virchow accordingly gave the name amyloid to the newly discovered substance. Several years later Friedreich and Kekulé showed that amyloid is a nitrogenous body of albuminous nature. According to the investigations of Krawkow amyloid is a firm combination of chondroitin-sulphuric acid with albumin.

The reactions of amyloid enable us to detect its presence in the tissues when it is present in such small amounts as to be otherwise invisible. In the microscopic examination of fresh preparations care should be
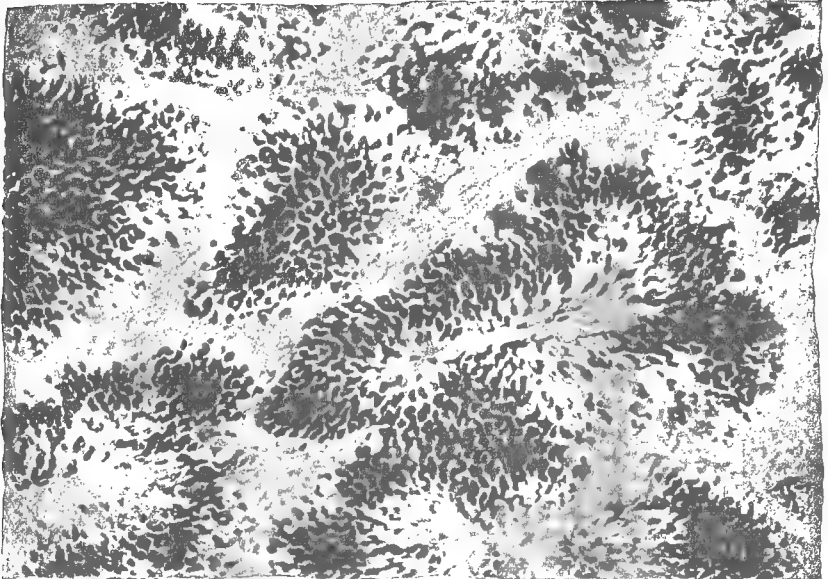
FIG. 68.—Section from an amyloid liver, treated with iodine solution. × 35.

taken to wash out the blood from the tissue, since the color resulting from the combination of blood and iodine may be deceptive.

Amyloid is resistant to acids and alkalies. Alcohol and chromic acid do not affect it; it is also resistant to putrefactive changes.

Amyloid is deposited *in the ground-substance of the connective tissue of blood-vessels, especially in the walls of the small vessels.* Living cells are not affected. In the connective tissue the amyloid substance appears first between the fibrillæ.

Amyloid degeneration as a rule is associated with diseases which are of hopeless chronicity and are characterized by the long-continued drain of albuminous elements from the blood and, in many instances, by the destruction of bone and cartilage. The condition is by no means as common now as formerly, since improved methods of treatment have tended to modify those diseases with which amyloid is most frequently associated. In 5,900 autopsies performed at Bellevue Hospital, amyloid degeneration occurred in 27 cases (0.5 per cent.) ; in 17 cases it was associated with ulcerative tuberculosis of the lungs, and in 10 of these

there were tuberculous ulcers of the intestine; in 6 cases amyloid was associated with ulcerative syphilides; in 2 cases with chronic suppurative pyelonephrosis; in one case with ulcerative carcinoma of the stomach; in another with chronic pyogenic osteomyelitis. The order of frequency with which the organs were involved was as follows: Spleen 23 times; liver 18; kidney 17; adrenals 7; gut, lymph nodes and heart once each.

In the acini of the liver the amyloid is found along the capillaries. The endothelium (Fig. 70, c) is covered on its outer side by a thick layer of a homogeneous, glassy substance, which may be broken up through numerous clefts into lumpy masses (c) of amyloid material. The liver-
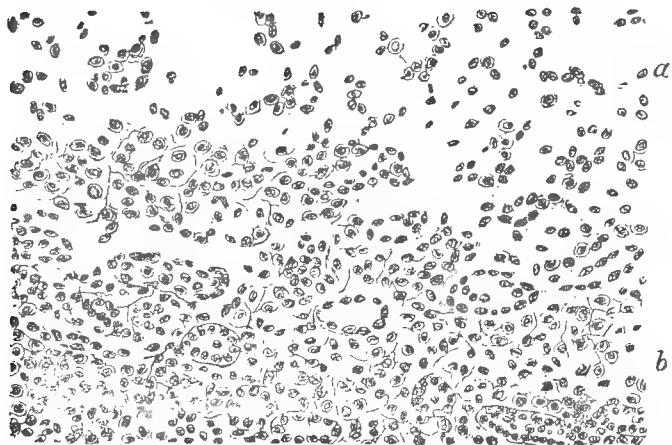
FIG. 69.—Amyloid degeneration of the splenic follicles and pulp. (Alcohol, methyl violet, hydrochloric acid.) a, Follicle showing marked degeneration; b, pulp showing beginning degeneration. × 300.

cells between the amyloid masses are either intact (a) or compressed (b), and atrophic, or may have disappeared. They often contain fat. The afferent blood-vessels of the liver, particularly the media of the arteries, may also show amyloid deposits.

In the kidneys (Fig. 71) the amyloid is found particularly in the vessel-walls. The capillaries of the glomeruli (b) may be thickened and homogeneous; likewise the arteries (i), the veins, and the capillaries (k) of other parts of the renal parenchyma may show amyloid deposits. In the intestinal mucosa the deposit is also found in the walls of the blood-vessels.

In fat-tissue, which is occasionally extensively involved, the amyloid substance is found in the vessel-walls, and in the connective tissue, and the membranous sheath of the fat-cells may be converted into a hyaline mass. In the spleen the connective-tissue trabeculæ (Fig. 69, a, b) and vessel-walls are especially likely to be affected, and may suffer marked thickening. In striped muscle the perimysium internum and the sarcolemma are involved. In glandular organs possessing a tunica propria, for example, the mucous glands and kidneys, this membrane may become greatly thickened.

The effects of amyloid degeneration on the functions of the affected organ are indicated by the degenerative and atrophic alterations in the

cells of the parenchyma. The connective tissue itself is permanently changed; the insoluble amyloid is never removed from it.

The deposit of amyloid substance in the blood-vessels leads to marked thickening of their walls, and to narrowing or even obliteration of their lumina (Fig. 71, *b*), and in this way to permanent disturbance of circulation. The amyloid masses may compress neighboring epithelial structures (Fig. 70) and cause them to atrophy. Often there is associated fatty degeneration of the epithelium (Fig. 71, *e, f*), particularly in the kidneys; this change is not to be referred wholly to the disturbances of circulation caused by the amyloid deposit. It is more likely that the
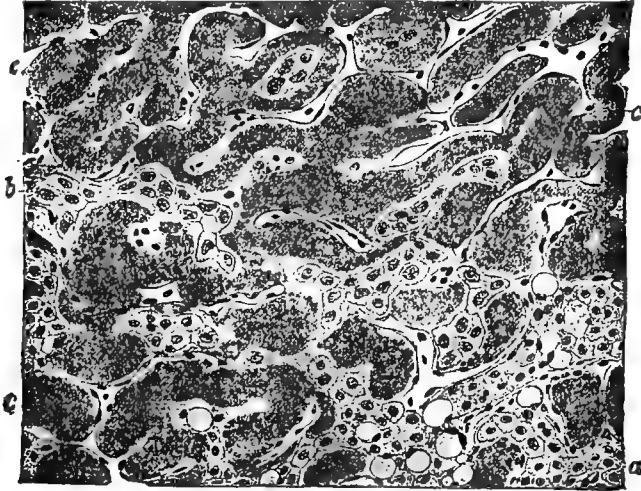
Fig. 70.—Amyloid degeneration of the liver. (Alcohol, Van Gieson's.) *a*, Liver-cells, in part containing fat; *b*, compressed liver-cells; *c*, amyloid. × 240.

fatty degeneration, at least in part, is a pathological process running parallel with the amyloid disease, and caused by the same conditions producing the latter. Consequently, in some cases the amyloid change may be slight, while the fatty degeneration is marked.

In the spleen and lymph nodes the lymphoid cells lying in the meshes of the thickened reticulum disappear as the result of atrophy. In muscles the contractile substance diminishes in proportion to the increase of the amyloid deposit in the intervening connective tissue.

Amyloid deposit is usually a sequel of cachexia due to *chronic ulcerative tuberculosis* of different organs, *chronic suppuration* (for example, of the bones), *syphilis* or *chronic dysentery*. In the cachexia of carcinoma it is but rarely observed. In rare cases the degeneration occurs without being associated with any of the above-mentioned diseases.

According to investigations by Czerny, Krawkow, Lubarsch, Davidsohn, Maximow, Nowak, Petrone, and Schepilewsky amyloid may be produced experimentally in the spleen, liver, kidneys, and intestines of various animals, rabbits, chickens, doves, mice, and dogs, through the production of suppurations lasting several weeks. Amyloid may develop also in horses that are inoculated with diphtheria bacilli. Suppurative processes caused by staphylococci and oil of turpentine appear in

particular to favor the formation of amyloid. In a number of cases amyloid was also successfully produced through injections of decomposed bouillon, dead cultures of staphylococci, rennet-ferment, and pancreatin (Schepilewsky), when the inflammation produced by these agencies ran a somewhat chronic course. Krawkow observed the beginning of amyloid formation after three days, Nowak after eight days.

The *origin of the amyloid substance* has not been definitely determined. The results of experimental investigation vary greatly, the degeneration often being absent in chronic suppuration (particularly in dogs). It is probable that the blood brings to the tissues some substance
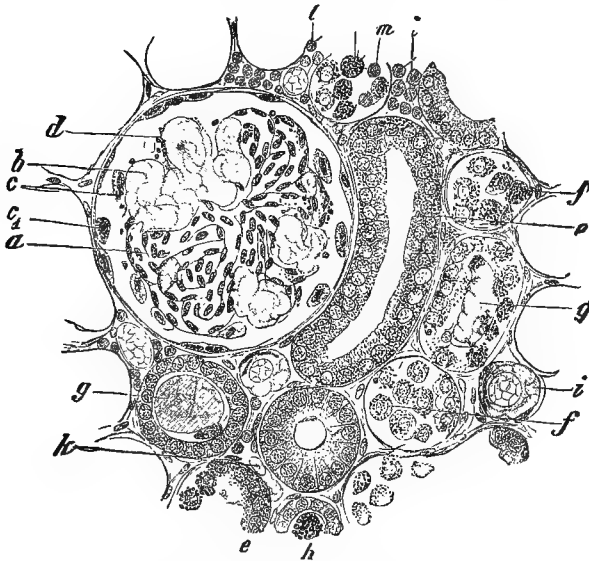
FIG. 71.—Section of an amyloid kidney. (Müller's fluid, osmic acid, methyl violet.) *a,* Normal vascular loops; *b,* amyloid vascular loops; *c,* fatty glomerular epithelium; c_1, fatty capsular epithelium; *d,* fat-drops lying against the outer surface of the capillary walls; *e,* fatty epithelium *in situ; f,* desquamated and fatty epithelium; *g,* hyaline coagula (cast); *h,* transverse section of a cast composed of fat-drops; *i,* amyloid artery; *k,* amyloid capillary; *l,* cellular infiltration of the connective tissue; *m,* round cells within the tubules. × 300.

which is changed into amyloid at the site of deposit. It has been many times shown that as the *antecedent of amyloid* there is found *a hyaline substance* in the tissues, which does not give the amyloid reactions. Similar observations have occasionally been made in man. The material from which amyloid arises is formed, perhaps, by disintegrating pus-cells or tissue-cells at the seat of the primary disease and thence enters the blood-stream.

According to *Krawkow,* there are found normally in the wall of the horse's aorta, in the ligamentum nuchæ of cattle, in the stroma of the spleen of calves, and in the mucous membrane of the stomach, combinations of chondroitin-sulphuric acid which are closely related to amyloid. According to *Neuberg,* amyloid proper is a basic albumin in the process of metamorphosis combined with chondroitin-sulphuric acid. From this last-named combination the basic albumin body may be easily differentiated chemically.

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§ 63. The form of amyloid degeneration just considered is a disease, which usually appears as an affection of several organs, or, if confined to a single organ, as a change extending throughout the whole organ. There is, however, a form of amyloid disease appearing as a *local infiltration of the tissues* or in the *form of free concretions.*

The **local amyloid infiltrations** occur in cellular granulations and in tissues showing chronic inflammatory processes; and in scars. They are also found occasionally in tumors in which other retrograde changes have begun. In certain cases only small deposits are found in the affected tissues, usually in the vessel-walls. In other cases larger nodules may be formed, and may acquire a wooden hardness.

Here also the *amyloid substance is deposited in the ground-substance of the tissue;* but it has been claimed by some authors (Rählmann) that the cells of the tissue

Fig. 72.—Corpora amylacea. *u,* Laminated prostatic concretions. × 200. *b,* Corpus amylaceum from an old hæmorrhagic infarct of the lung, with hæmatoidin crystals in its nucleus. × 200. *c,* Corpora amylacea from the spinal cord. × 400.

may acquire a hyaline appearance and give the amyloid reactions.

Such local infiltrations of amyloid have been found in the inflamed conjunctiva, in syphilitic scars of the liver, tongue, and larynx, in inflamed lymph nodes, in the urinary bladder, ulcers of the leg, and in tumors of the larynx and stomach. **Tumor-like nodules of amyloid** also occur in the conjuctiva, tongue, larynx, lymph nodes, and trachea under conditions in which it is impossible to establish any relationship between them and inflammatory processes, and where besides the hyaline masses there is but little normal connective tissue present. According to Burow, Manasse, von Schrötter, Zahn, and others, such nodules may arise also from connective-tissue tumors.

Free concretions or **corpora amylacea** occur most frequently in the tissues of the central nervous system, especially in the substance of the spinal cord, and in the ependyma of the ventricle. They are found also in the prostate. In the nervous system they appear as small (Fig. 72, *c*), dull-shining, mostly homogeneous bodies, more rarely consisting of a

nucleus and an outer shell (Redlich); in the prostate they form larger (Fig. 72, *a*) bodies which usually show distinct stratification. Corpora-amylacea have also been found in carcinomata (Wagner, Langhans), and have been repeatedly observed in the lung, where they occur in inflammatory areas, hæmorrhagic extravasations (*b*), and in emphysema.

Corpora amylacea cannot be regarded as of the same nature as the progressive amyloidosis of connective tissue. Some of them, it is true, give characteristic amyloid reactions, and the corpora amylacea of the nervous system, in particular, become blue or brownish-violet when treated with iodine and sulphuric acid. But, in the case of these bodies, we have to do with formations which are dependent on local conditions for their origin; and are derived in part from epithelium, and in part from connective-tissue cells. They are, therefore, to be regarded as modified epithelial (§ 60), or connective-tissue hyalin (§ 65). The prostatic concretions are formed through the fusion of degenerating epithelial cells (epithelial colloid, § 60); similar bodies found in the lungs and in tumors are likewise composed of disintegrated cells, though in part of albumin derived from the blood. The corpora amylacea of the nervous system probably arise from fragments of swollen axis-cylinders to which, perhaps, remains of the medullary sheath still cling.

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XII. Hyaline Degeneration of Connective Tissue and the Hyaline Products of Connective-tissue cells.

§ 64. Under the head of **hyaline degeneration of connective tissue** may be grouped those changes in which the *fibrous ground-substance acquires a hyaline character without giving the specific reactions of amyloid* (Fig. 73). The change may involve connective tissue, altered by chronic inflammation, as well as the newly formed connective tissue of inflammatory lesions and the stroma of tumors. Hyaline degeneration is found most often in the connective tissue of the thyroid (Fig. 73, *b*); the valvular endocardium; intima of the arteries; the entire wall of the smaller vessels, particularly of the brain and spinal cord; the lymph nodes (Fig. 75, *a*, *b*); glomeruli of the kidney; the connective tissue and blood-vessels of tumors of the dura mater (psammoma), parotid, and submaxillary glands (angiosarcoma); the connective tissue of scars; the peripheral portions of tuberculous nodules; the connective tissue of chronically inflamed tendon-sheaths and bursæ (Fig. 74, *b*).

Hyaline degeneration of connective tissue possesses no specific staining reactions, as does amyloid. Staining with Van Gieson's acid fuchsin and picric acid gives to hyalin in the great majority of cases an intense fuchsin red; but this reaction is sometimes wanting. It is probable that the transformation of connective tissue known as hyaline represents a variety of degenerative conditions.

In many cases (hyalinisation of the heart-valves or of the intima of arteries) the tissue appears on microscopic examination to be thick, homogeneous and poorly nucleated, and the condition has been designated **sclerosis.** The gradual disappearance of the nuclei, the subsequent calcification or softening even to the point of complete disintegration (for example in sclerotic areas of the intima), the sequestration of the altered tissue from the normal (for example, in the degenerated portions of the walls of bursæ), all point to the fact that the process is degenerative in character.

In other cases the appearance of the hyaline tissue resembles closely that of amyloid degeneration, and there is associated with the hyaline change a pronounced increase of bulk, particularly in the small vessels of the central nervous system, of the spleen, renal glomeruli

FIG. 73.—Hyaline degeneration of the connective tissue of a colloid goitre. (Alcohol, Van Gieson's.) *a*, Follicles containing colloid; *b*, hyaline connective tissue; *c*, blood-vessel. × 300.

and lymph nodes, more rarely in the connective tissue itself. There occur moreover, though rarely, certain forms of hyaline degeneration involving the heart (Fig. 76, *b*, *c*), serous membranes, intestinal wall, etc., with the formation of glassy masses, which in part give the amyloid reaction, and in part do not. In proliferations of the conjunctiva there frequently has been observed hyaline degeneration of the reticular ground-substance with nodular thickenings; this material gives the amyloid reaction only in part. It may therefore be assumed that there is a form of hyaline degeneration of connective tissue which is closely related to amyloid, and may become changed into the latter; and that it arises through the deposit of a hyaline insoluble albuminous body probably derived from the blood.

FIG. 74.—Hyaline degeneration of the connective tissue of the wall of a tuberculous bursa. (Müller's fluid, hæmatoxylin, and eosin.) *a*, Fibrous connective tissue; *b*, hyaline connective tissue. × 40.

The preparation shown in Fig. 76, was taken from the heart of a woman of fifty-five years of age, the greater part of the heart-wall presenting hyaline

degeneration. In both endo- and pericardium there were numerous hyaline nodules and flattened masses. The muscle tissue was in part degenerated, as shown in the figure. Associated with this condition there was extensive degeneration of the blood-vessels, particularly of the intestines, tongue, lungs, heart and urinary blad-
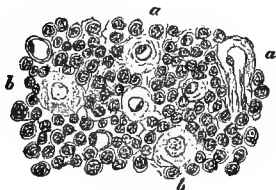
FIG. 75.

FIG. 76.

FIG. 75.—Hyaline degeneration of the blood-vessels of an atrophic axillary lymph-node. (Alcohol, carmine.) *a,* Hyaline vessel with open lumen; *b,* obliterated vessel. × 200.
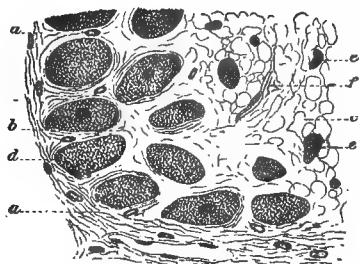
FIG. 76.—Hyaline degeneration of the connective tissue of the myocardium. (Alcohol, hæmatoxylin, carmine.) *a,* Normal connective tissue; *b,* hyaline connective tissue; *c,* hyaline masses; *d,* transverse section of normal muscle-cells, of atrophic (*e*). × 250.

der. The peritoneum was also thickly covered with hyaline nodules. The fact that the small areas and the periphery of the larger ones gave no iodine-reaction, while the central portions of the larger areas did so, appears to point conclusively to a close relationship between hyaline degeneration and amyloid. A similar case has been described by Steinhaus.

§ 65. **Hyaline products** arise from certain spherical masses of *connective-tissue cells arranged in concentric layers,* which, in a manner similar to the cornification of epithelial cells, become changed into *a hyaline substance containing no nuclei.* These formations occur most frequently in the meninges, the choroid plexus, and the pineal gland, and in the new-growths arising in these regions. Through subsequent calcification they lead to the formation of laminated concretions (see § 66, Fig. 84).
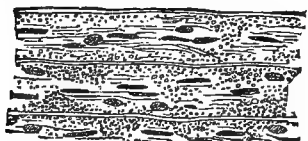
FIG. 77.—Calcification of the media of the aorta. × 350.

Another kind of hyalin possibly owes its origin to secretory activity of connective-tissue cells. This may be designated *secretory connective-tissue hyalin,* but it must be noted that the *cells themselves may be converted into hyaline products.* The variety of hyalin is perhaps oftenest observed as red-staining spherules lying free in the tubules of chronically inflamed kidneys. The fuchsinophile bodies of Russell were formerly included in the same category, but are now regarded as phagocytised red corpuscles which have undergone hyaline transformation.

Von Recklinghausen gives to the term *hyalin* a more comprehensive meaning than *Ziegler.* He includes under hyaline degeneration pathological changes which Ziegler placed under other heads. He defines hyalin as an albuminous body which stains intensely with eosin, carmine, picrocarmine, and acid fuchsin; is homogeneous and strongly refractive; is but slightly changed by acids; and in its resistance to alcohol, water, ammonia, and acids resembles amyloid, but does not give the iodine reaction. As hyalin he includes epithelial colloid and the hyaline products of connective tissue cells, as well as hyaline degeneration of the ground substance of the

connective tissue, also hyaline thrombi, and the hyaline coagula of inflammatory exudates, and hyaline tissue-necroses. According to Von Recklinghausen all of these formations result from the fusion of the elements of neighboring cells. From their external appearance, all may be designated *hyalin;* but the following varieties must be recognized: *epithelial hyalin* (colloid, keratohyalin), *connective-tissue hyalin* (hyaline degeneration of the ground-substance of connective-tissue, hyaline products of cells, and cells which have become hyaline), *blood-hyalin* (hyaline thrombi), *exudative hyalin* (hyaline coagula of exudates on mucous membranes, serous surfaces, inflamed connective tissue, in the urinary tubules, tubercles, etc.), and *hyaline tissue-necroses.* In the case of connective-tissue hyalin a distinction must be made between the hyalin formed as a secretion in the cells (closely related to epithelial colloid, in its mode of origin), and hyaline degeneration of the ground-substance of connective tissue.

XIII.   Petrifaction of Tissues and the Formation of Concretions and Calculi.

§ 66. It is of rather frequent occurrence for firm crystalline or amorphous masses to be deposited in various parts of the body; and when the deposits are of such extent as to cause hardening of the affected tissue, the resulting condition is known as **petrifaction,** or when the deposit consists of lime-salts (particularly carbonates and phosphates) as **calcification.**.

The deposit may occur, in the first place, in a tissue which forms an integral element of an organ, and which bears its normal relation to the surrounding tissues. In other cases it takes place in portions of tissue which have been loosened from their surroundings; or in insoluble sub-
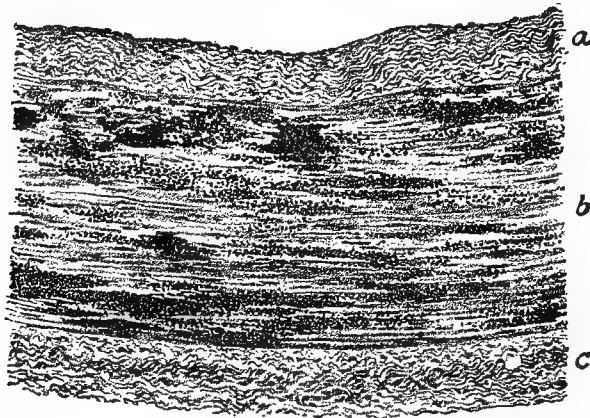
FIG. 78.—Calcification of the media of the femoral artery. (Silver preparation.) *a,* Intima; *b,* media; *c,* adventitia. × 40.

stances which have become changed into a firm state; or, finally, in foreign bodies which have entered the body from without, and form the centres of a process of incrustation.

In the first case there arise **petrifactions of the tissues;** in the second, **free concretions and calculi.** It is to be noted, however, that under certain conditions free concretions may become firmly attached to the tissues of the organ in which they lie, by means of tissue-proliferations extending into or surrounding them. On the other hand, a calci-

fied portion of tissue may in the course of time gradually become loosened from its surroundings and ultimately form a free concretion.

Deposit of lime salts occurs in the form of fine colorless granules (Fig. 77) which when treated with silver (von Kossa) take on a black color (formation of silver phosphate) (see Figs. 78, *b*, 80, and 81, *B, b*). When closely crowded they become confluent, and give rise to chalky foci (Fig. 78, *b*) that are usually not sharply circumscribed; they
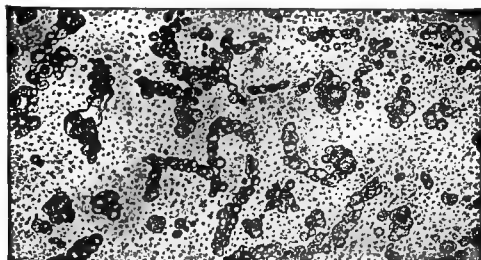
FIG. 79.—Calcified vessels in the cerebellum.   (Alcohol, hæmatoxylin.)   × 100.

may form also circumscribed spherical concretions (Fig. 79). In the blood-vessels calcification may begin either in the connective tissue, muscle-fibres, or in the elastic tissue.

The *cause of petrifaction is to be found in local tissue-changes,* in that the deposit of lime-salts occurs in places where the tissue has already died or is in process of degeneration. For example, lime salts may be deposited in pulmonary infarcts (Fig. 80), in thrombi, in ne-
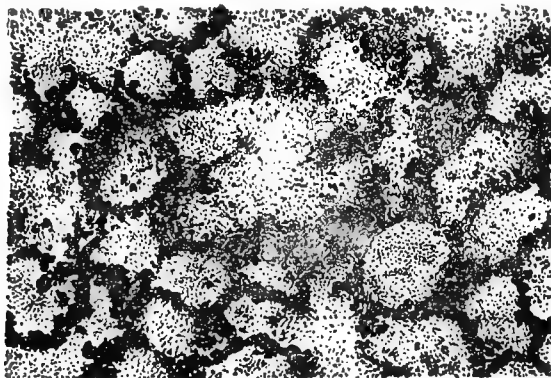
FIG. 80.—Calcification of a necrotic lung in the periphery of a hæmorrhagic infarct six weeks old.   (Formalin, silver treatment.)   × 100.

crotic foci arising during the course of inflammations, in dead cells, particularly renal epithelium (Fig. 82, *d, e*), and liver-cells (von Kossa) that have been killed as the result of intoxications (mercuric chloride, lead, aloin, bismuth, copper salts, iodine, and iodoform). A frequent antecedent to the deposit of lime-salts is hyaline degeneration of connective tissue, often associated with a deposit of fat. This occurs in the thickened intima of the blood-vessels and heart-valves, in the media of the medium-sized arteries, particularly in the extremities, in inflammatory new-formations of connective tissue (for example, in the serous

membranes), in the connective tissue of the kidney pyramids of old people (Fig. 81, A, B), and in degenerated thyroid glands. In dying adi-
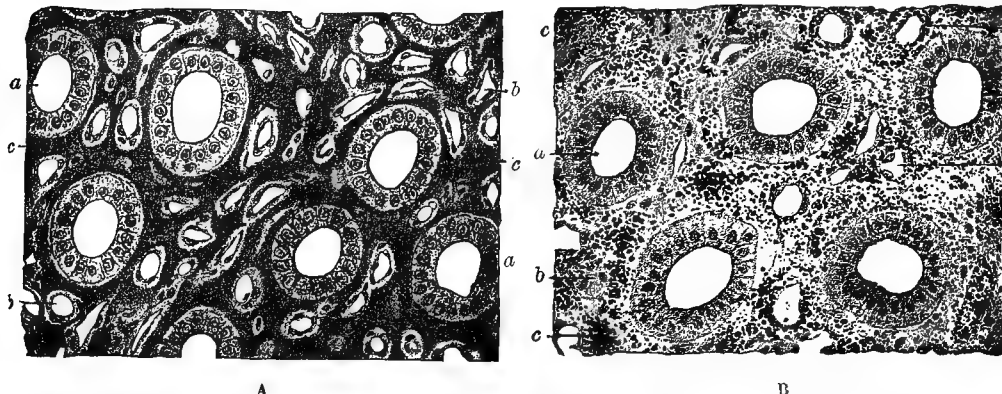
Fig. 81.—Hyaline degeneration and calcification of the connective tissue of the kidney papillæ. A, Stained with hæmatoxylin and eosin. B, Treated with silver nitrate. *a*, Collecting tubules; *b*, blood-vessel; *c*, connective tissue showing hyaline degeneration and calcification. × 300.

pose tissue (fat necrosis in the neighborhood of the pancreas) chalky soap may be formed.

The hyaline character of the degenerated connective tissue shows well both in staining with Van Gieson's and with simple hæmatoxylin. With the latter stain the calcified connective tissue becomes a diffuse dark blue color (Fig. 81, *A, c*). The same staining reaction occurs in calcified necrotic cells (Fig. 82, *d, e*). This reaction holds good only for the deposit of carbonates and phosphates, but not for the oxalates of lime.

In rare cases there may occur a deposit of lime-salts in organs which show but slight changes — for example, in the lungs. Since in such cases there is destruction of bone— osteomalacia, caries, tumors, etc.— this deposit is regarded as metastatic in nature, due to the over-loading of the blood with lime salts. Even under these circumstances the immediate cause of the calcification is local, and is dependent on retrogressive changes; the increased absorption of bony structures is but a favoring factor. According to investigations of Kockel and Kischensky the elastic lamellæ of the small and medium-sized vessels in particular become calcified, but the elastic fibres and capillaries of the pulmonary interalveolar septa are also involved.
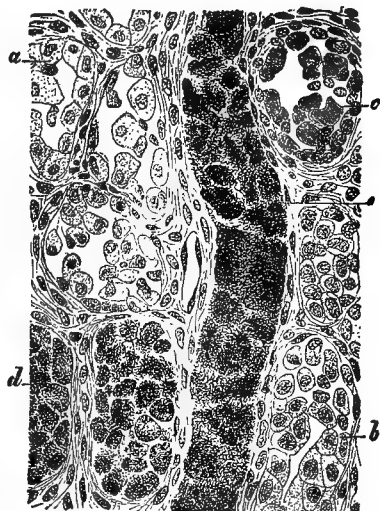
Fig. 82.—Calcification of the epithelium of the kidney-tubules following sublimate poisoning. (Alcohol, hæmatoxylin.) Patient died seven days after the poisoning. *a*, Normal tubules; *b*, tubule with desquamated epithelium; *c*, tubule with desquamated and necrotic epithelium possessing no nuclei; *d, e,* tubule with degenerated and calcified epithelium. × 300.

The calcification may affect either small or large areas, and in the latter case causes hardening and white coloration of the tissues. Occasionally it appears in the form of sharply circumscribed spherical, or nodular (Figs. 83 and 84, *a*, *b*, *c*), or long spicule- (Fig. 84, *d*), or cactus-like formations, and there arise in consequence **concretions in the tissue** that occasionally may be recognized with the naked eye. Under physiological conditions such concretions are found in the form
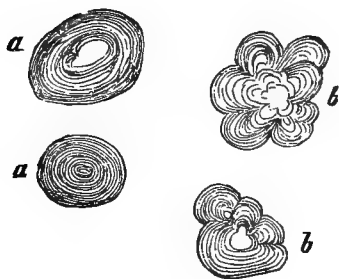
FIG. 83.
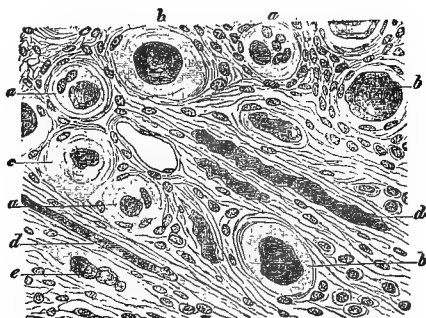
FIG. 84.

FIG. 83.—Calcareous concretions. *a*, Concretions from an inflamed omentum; *b*, calcareous masses from a tuberculous lymph-gland which had undergone caseation. × 200.
FIG. 84.—Section from a psammoma of the dura mater, with concretions. (Alcohol, picric acid, hæmatoxylin, eosin.) *a*, Hyaline nucleated spherule with enclosed calcareous granule; *b*, calcareous concretion with hyaline non-nucleated capsule, embedded in fibrous connective tissue; *c*, calcareous concretion surrounded by hyaline connective tissue; *d*, calcareous spicule in connective tissue; *e*, calcareous spicule containing three separate concretions, embedded in the connective tissue. × 175.

of laminated chalky spherules in the pineal gland and choroid plexus, forming the so-called brain-sand (acervulus cerebri). As pathological formations they occur in different regions, in tumors of the meninges known as psammomata, in caseous masses or in indurated connective tissue (Fig. 83, *a*). The origin of these formations may best be studied in the psammomata and is to be referred to transformation of tissue cells (Fig. 84, *a*, *b*, *c*), or of fibrous connective tissue (*d*) into a hyaline mass that at first may contain nuclei (*a*), and later loses them (*b*, *e*), and takes up lime-salts. Spherical concretions arise chiefly from hyaline masses formed from cells (*a*, *b*, *c*); spicules (*d*) arise through the calcification of hyaline connective tissue, but spherical concretions (*e*) may also arise in hyaline connective tissue.

Formation of bone or **ossification** may follow the calcification of a tissue, either as the result of new tissue-formation, or of metaplastic *development of osseous tissue*. This has been observed in the media of calcified blood-vessels of the extremities and in the aorta, but may occur also in calcified lymph-nodes, in the neighborhood of calcified necrotic areas in the lungs, and in thickened serous membranes, etc. One of the most striking examples of the latter form of involvement is complete calcification and ossification of the tunica vaginalis testis.

According to the investigations of *Gierke*, calcifying tissues (fœtal bones, the enamel of the dentine, sand bodies of the choroid plexus, placental calcifications,

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calcified ganglion-cells) contain more or less iron, and there occur also iron-containing cell-necroses (epithelial casts in sublimate poisoning) which stain like calcified tissue, but are not calcified. In other cases (fully developed bone in extrauterine life, calcified thrombi and calcified vessels) iron is not present.

Klotz (*Jour. of Exper. Med.*, 1905, 1906) suggests that the formation of calcium soaps is the first step in the formation of pathological masses of calcification, these soaps later undergoing transformation into the less soluble phosphate and carbonate.

Wells (*Jour. of Exper. Med.*, 1905) found but minute traces of calcium soaps in calcifying matter. It is therefore, probable that calcium-soap formation may be an important step in the process of pathological calcification, but is not an essential one. The especial affinity of calcium for cartilage, hyaline connective tissue, etc., cannot at present be explained.

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§ 67. The more common petrifactions consist of deposits of phosphate of lime, sometimes of carbonate; with these magnesium salts may be mixed. Under special conditions there occur **deposits of uric-acid salts;** particularly in the disease known as **gout,** which is a disturbance of general nutrition characterized by the deposit of uric acid in the tissues.

Gout is usually inherited, rarely acquired; it occurs frequently in certain regions, for example, in England and in North Germany; and is rare in other countries, as South Germany. Of the cause of the disease we have no positive knowledge. It is characterized by the deposit of uric-acid salts, chiefly sodium urate, with which small quantities of carbonate and phosphate of lime are sometimes associated. The deposit of these salts usually takes place during acute paroxysms characterized by pain and inflammation, but departures from a typical course may occur. The deposits are found in the kidneys, skin, subcutaneous tissue, tendon sheaths, tendons, ligaments, bursæ, and articular cartilages, but may finally involve almost all the organs. The metatarsophalangeal joint of the great toe is the *favorite site of deposit,* and often the first part affected. The deposits consist of clusters of slender needles (Fig. 85), in whose neighborhood the tissues are degenerate or necrotic; from this it may be assumed that the urates entering the tissues in solution give rise to necrotic changes in the latter.

The areas of necrosis and incrustation are at first of small size, but occasion inflammation and tissue-proliferation in their neighborhood.

With the occurrence of other paroxysms the deposits become larger, so that *nodules* (the so-called *tophi*) are formed. These consist of white, plaster-like masses, and may form marked thickenings in the joints and tendons (Fig. 86).
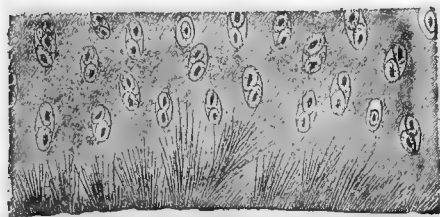
In the joints the articular cartilages appear as if sprinkled with plaster-of-Paris, but later the white masses may permeate the entire articular cartilage. In the kidneys necrosis and inflammation may lead to contraction and induration of the organ. The deposit affects chiefly the medullary pyramids, but is also found in the cortex.

According to Garrod and Ebstein the acute paroxysms in gout depend on excessive accumulation of uric acid, either as the result of deficient excretion by the kidneys (Garrod) or of local changes (Ebstein). According to Pfeiffer the gouty predisposition is due to the fact that the uric acid in the body-fluids is produced in a form which is soluble with difficulty, and is deposited in the tissues in such quantity as to cause localized necrosis. The symptoms of the gouty paroxysm are supposed to depend on increased alkalinity of the body-fluids and as a result there follows partial solution of the deposited uric acid, in the course of which pain and inflammation are produced. On the other hand, von Noorden regards the formation and deposit of uric acid as a secondary process, due to the local action of a special ferment, and quite independent of the amount and condition of the uric acid in other parts of the body.

§ 68. **Free concretions** are formed in various ducts and cavities which are lined
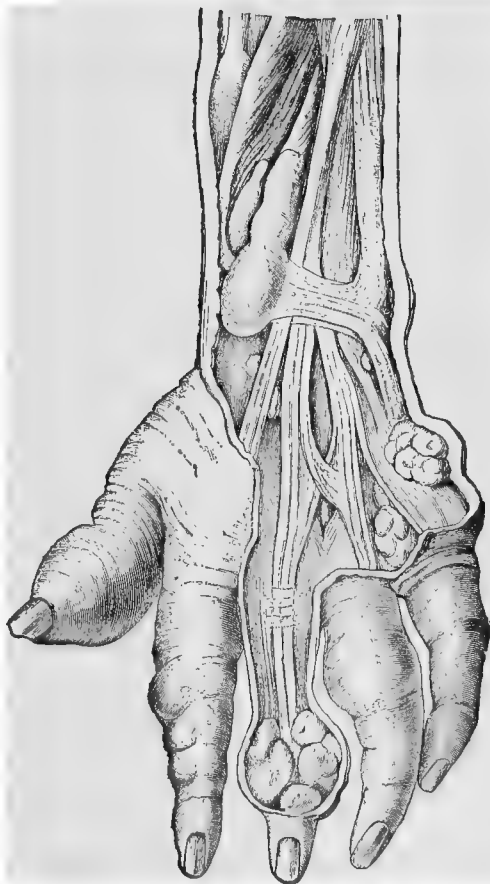
FIG. 86.—Gouty nodes of the hand. (After Lancereaux.)

by epithelium, as in the intestines or in the ducts of glands pouring their secretions into the intestine, in the gall-bladder, urinary passages, and respiratory tract. The concretions formed in the blood-vessels and serous cavities might also be included in this group, although they are for the greater part united to the surrounding tissues.

All free concretions possess an organic base or nucleus. Thus *enteroliths* which form in the intestines have a nucleus of inspissated fæces, or foreign bodies which have been swallowed, such as hairs (*bezoar stones* or *ægagropilæ*), or indigestible portions of vegetable food, etc., in and about which phosphates (ammonium-magnesium and calcium phosphate), and carbonates are deposited. In the mouth incrustations of the teeth, known as *dental calculi* or *tartar*, are formed by the deposit of lime-salts in masses of mucus, cell-detritus, and bacteria. In the same way there are formed in the *ducts of the salivary glands and pancreas* oval or spherical faceted, or irregularly nodular *concretions,* through the calcareous impregnation of substances derived from the epithelium of the gland.

FIG. 87.—Faceted stones from the gall-bladder. Natural size.

Bronchial calculi are formed by the calcification of thickened secretion; the *stones found in veins and arteries* (phleboliths and arterioliths) from the calcification of thrombi; *prostatic calculi* through the calcification of the so-called amyloid concretions; *navel stones* through the incrustation of desquamated epithelium, hairs, and other substances which enter the navel-depression.

FIG. 88.—Section through a small cholesterin stone after removal of the cholesterin. × 13.

The *biliary calculi* or *gall-stones* found in the bile passages and gall-bladder are small granules, or larger spherical, oval, or faceted stones (Fig. 87), which on fracture appear to consist purely of crystalline masses. By proper methods it may be shown that these stones also possess a nitrogenous ground-substance.

According to their composition gall-stones may be classed as cholesterin, cholesterin-pigment, bilirubin, biliverdin-calcium, and calcium carbonate stones. The first two varieties are the most common; they

present a rayed, crystalline, often laminated fracture; and vary in color and mottling according to the amount of bile-pigment present. When no pigment is present they may be colorless and translucent.

If the cholesterin be dissolved out of a stone, it will be found that
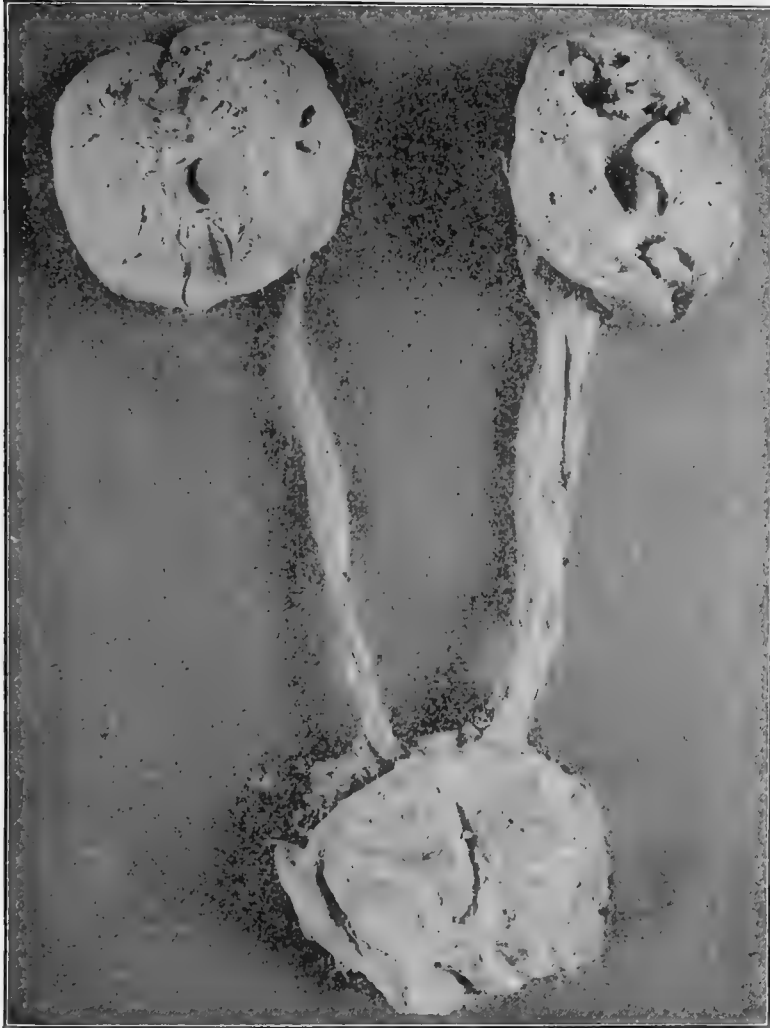
FIG. 89.—(Bellevue Hospital.) Stones in left kidney; secondary distention and tortuosity of both ureters; gangrenous cystitis.

the form of the stone is preserved, and a delicate yellowish mass remains. This, when cut into sections, is found to consist of a homogeneous substance (Fig. 88) with concentric stratification and radiating clefts or spaces which were formerly occupied by the crystal-

line masses.   A similar ground-substance may be demonstrated in other calculi after solution of their calcium salts.

The majority of all gall-stones are the result of the incrustation of an organic substratum, derived from the mucous membrane of the biliary passages and the gall-bladder, following injury produced by infections, most commonly the typhoid and colon bacilli.   Thus gall-stones may be brought about experimentally by injecting typhoid bacilli into the blood stream after mechanical injury of the mucosa of the gall-bladder, and living bacilli may be demonstrated in gall-stones long after the subsidence of typhoid fever.   Inflammation of the bile-passages (angiocholitis) leads to desquamation and destruction of the epithelium, and in the products derived from these changes bilirubin and cholesterin are deposited.   When once a concretion is formed it increases in size through new products of cell-disintegration which become encrusted with cholesterin, pigment, and calcium.   According to Naunyn the original nucleus of the concretion undergoes a change, in that it separates into fluid, and into firm, granular masses of pigment, calcium, and crystals of cholesterin which are deposited on the outer crust, so that the stone contains a cavity filled with fluid. In the course of time this fluid may be replaced by cholesterin, as may the pigment and calcium in the remaining portions of the stone.   In addition calcium carbonate may be deposited.

FIG. 90.—Uric-acid infarct of the new-born.   (Alcohol, hæmatoxylin.   Drawn from a preparation that had been washed in water.)   Transverse section through the pyramid of the kidney.   *a*, Transverse section of unchanged collecting tubule from the papilla; *b*, dilated collecting tubule filled with uric-acid concretions; *c*, remains of concretions after washing with water.   × 200.

The cholesterin masses from which the concretions are formed are derived from the disintegration of epithelial cells; likewise, the lime-salts combining with bilirubin are furnished by the mucous membrane.

The *urinary calculi, gravel,* and *stones* are also composed of an organic ground-substance in which various constituents of the urine become deposited.   According to location we may distinguish calculi of the kidney and those of the descending urinary passages.   In the kidneys the deposits may form small granules lying in the tissue itself, or free in the lumen of the urinary tubules in products derived from the disintegration of epithelial cells.   This is true of the calcifications which, as mentioned above, occur in necrosed renal epithelium after poisoning with corrosive sublimate, bismuth, aloin, copper-salts, iodine, phosphorus, potassium chromate, and oxalic acid, and also applies to some of the gouty deposits.   The so-called *uric-acid infarct of the new-born,* a condition characterized by the appearance of yellowish-red stripes in the medullary pyramids, also belongs in this category.   The condition is not infrequently seen in children dying during the first few weeks after birth.

The epithelium of the tubules is usually well preserved, but in places desquamation and disintegration of cells may be found. The lumina of
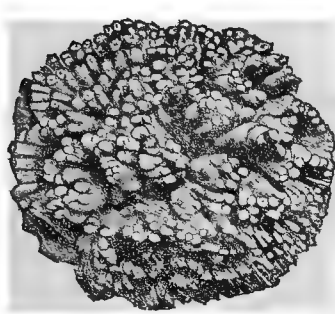
Fig. 91. Fig. 92.

Fig. 91.—Coral-shaped stone from the bladder composed of calcium oxalate and phosphate. Natural size.
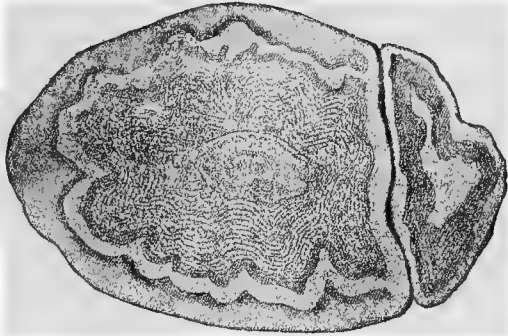
Fig. 92.—Transverse section of two stones from the bladder, closely fitted together, and consisting of sodium urate and ammonium-magnesium phosphate. Natural size.

Fig. 93.—Incrusted lead-pencil, 12 cm. long, taken from the male urinary bladder. Reduced 1/10.

the tubules are filled with small, colorless or yellow granules of urates or uric acid, which at times show fine radiating lines (Fig. 90, b). On solution of these granules a delicate stroma remains (c). If from the presence of the infarct further changes in the epithelium are produced, leading to the formation of albuminous material in the tubules, single granules may develop through accretion into large stones, but this is rare.

In the pelvis of the kidney, in the ureters, urinary bladder, urethra, and under the prepuce, concretions may be formed, as sand, gravel, or stones. The last-named are oval or spherical, and smooth, or rough and nodular, not infrequently resembling a mulberry or mass of coral (Figs. 91 and 92). When several stones lie close together, their surfaces may become faceted (Fig. 87). Those found in the kidney may form casts of its pelvis and of the calyces.

When examined in section, urinary calculi are sometimes homogeneous, at other times stratified (Fig. 92) or show radiating lines. Not infrequently there may be seen a nucleus and several zones of different appearance. The crystalline masses lie partly in the spaces of the stroma, and partly in the latter itself; it may be assumed that the stroma is a product of the mucosa of the urinary passages, and that its formation follows catarrhal inflammations or necroses of epithelium leading to the collection of mucus or cell-detritus in the tubules.

What substances are deposited in the products of the mucous membrane depends on existing conditions. If the excretion of uric-acid salts by causing tissue-necrosis has produced conditions favoring

the development of concretions, the deposits in the organic ground-substance consist chiefly of urates. Decomposition of urine with the formation of ammonium-magnesium phosphate leads to calculi consisting chiefly of this substance. Cystin calculi may be formed when cystin is excreted by the kidneys, as the result of inability on the part of the tissues to decompose it. Once a stone is formed, the irritation which it causes, as well as decomposition of the retained urine, favors growth by accretion. Likewise, *foreign bodies* (Fig. 93), which have entered the bladder from without, may *lead to the formation of calculi.*

Intestinal calculi are more common in horses and cattle than in man; undigested vegetable material and hairs which have been licked off and swallowed form the starting-point of such concretions. The true stones, which occur especially in horses, are rather hard masses consisting chiefly of magnesium phosphate; the false stones consist of hairs and vegetable fibres which are more or less encrusted. Occasionally balls are found which consist almost wholly of hair (*ægagropili* or *bezoar stones*). In ruminating animals they are found in the rumen or reticulum; in hogs, in the small intestine.

According to *Schuberg,* the enteroliths of herbivorous animals consist chiefly of carbonates; those of carnivorous, of phosphates. The composition of those found in man varies according to the food ingested.

Urinary calculi are classified according to their composition as follows:

1. *Calculi composed chiefly of uric acid or urates.*

Pure *uric-acid* calculi are usually small, yellow, reddish, or brownish in color, and hard.

Stones consisting of urates are rarely pure. They are usually covered on the surface with a coating of calcium oxalate and ammonium-magnesium phosphate.

2. *Calculi composed chiefly of phosphates and carbonates.*

To this class belong stones composed of *calcium phosphate, ammonium-magnesium phosphate,* and *calcium carbonate.* The last two varieties are rare. All these calculi are white or grayish-white. The triple phosphate stones are soft and friable, the others hard.

3. *Stones composed of calcium oxalate.*

These are hard and rough, and of a brown color.

4. *Cystin calculi.*

These are soft, waxy, and of brownish-yellow color.

5. *Xanthin calculi.*

These are cinnebar-red in color, smooth, and have an earthy fracture.

Ebstein and *Nicolaier* succeeded in producing urinary calculi by feeding animals with oxamide, an ammonium derivative of oxalic acid. The greenish-yellow concretions thus produced in dogs and rabbits consist essentially of oxamide; on section they present a concentric laminated structure showing radiating striations. They possess an albuminous stroma derived from the necrosis and desquamation of epithelium caused by the action of the oxamide during excretion.

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XIV. The Pathological Formation of Pigment.

§ 69. Both connective and epithelial tissues in various parts of the body normally contain **autochthonous pigment,** which *lies in the cells,* and consists of yellow, brown, or black granules, or gives a diffuse yellow or brown color to the cells. The autochthonous pigments are **melanin, lipochrome** and **hæmofuscin.**

Melanin is found in the lower cells of the rete Malpighii, in the coloring matter of the hair, and in the choroid coat of the eye and retina. In the pigment-cells of the skin the granules are chiefly yellow and brown; in the retina they are black.

The **autochthonous pigments may be increased** under various physiological and pathological conditions. For example, *during pregnancy the pigment of the skin is more or less increased* (*chloasma uterinum*), particularly in brunettes. In *Addison's disease,* which is dependent on pathological conditions of the adrenals (see § 26), there occurs decided pigmentation of the skin as a result of increase of the normal pigment. Not infrequently spots of a bronze color appear in the mucous membranes of the mouth and elsewhere.

Intense grades of pathological pigmentation are met with in *freckles, lentigines, pigmented moles* (Fig. 94) and *warts,* and in *melanotic tumors* (see Chapter VIII.) The pigment is melanin, and the amount may be so great as to give the tissues a pure black color.

The pigment lies for the greater part in the cells (*chromatophores*), more rarely in the intercellular substance. It is composed of yellow, brown, or black granules; not infrequently individual cells may be diffusely pigmented. In Addison's disease the granules are found partly in epithelial cells, especially in those lying directly on the connective tissue (Fig. 95, A, *a*, *b*, and B, *a*), and partly in branched chromatophores (A, *c*, c_1, *d*), whose pigmented processes extend up between the epithelial cells (B, *c*).

Fig. 94.—Large hairy pigmented mole over the back and buttocks, with scattered spots of pigmentation over trunk and shoulders. (After Röhring.)

In pigmented spots in the skin and in melanotic sarcomata the pigment is contained in specially differentiated connective-tissue cells of large size, and in cells of apparently normal size for the given tissue, often in connective-tissue cells in the neighborhood of vessels and in the vessel-walls.

The pigments described are products of specific cell-activity; and we must suppose that many cells form pigment from the material brought to them. In the majority of cases the pigment appears to be formed in

the places where it is found; yet different investigations make it probable that the pigment may at times be transported. The pigment of the epidermis and of the hairs, at least in part, is not formed in the epithelial cells themselves, but in branched connective-tissue cells, or chromato-phores. (Fig. 95, A, *c, d,* and B, *c*) which lie just beneath the rete, and send processes between the epithelial cells, through which the pigment is transferred to the latter.

The fact that the pigment is often found about the blood-vessels would seem to indicate that the material from which it is formed is derived from the blood, and this view was once accepted by many. Against it is the fact that neither in the blood nor in the neighborhood of the blood-vessels are there evi-dences of the disintegration of red cells, and the theory of hæmatogenous derivation now finds little if any favor.

The attempt has been made to solve the problem by chemical investigations; and the results obtained favor the theory that the pigment is a product of cell-activity, and is formed from albuminous bodies. The different forms of **melanin,** in which group the pigments of the skin and choroid are placed, are, ac-cording to the investigations of von Nencki, Sieber, Abel, Davids, and Schmiedeberg, nitrogenous bodies rich in

FIG. 95.—*A,* and *B,* Pigmented cells of the skin from a case of Addison's disease with caseous tuber-culosis of both adrenals. (Alcohol, carmine.) *a,* Pigmented epithelium cells from the deepest layer, in a section cut at right angles to the surface. *A, b,* Pigmented epithelial cells from a section made parallel to the surface. *B, b,* Epithelial cells con-taining no pigment; *c, c₁,* nucleated pigmented con-nective-tissue cells, the processes of which, in *B,* push between the epithelial cells; *d,* pigmented cell-processes. × 350.

sulphur, but vary greatly in composition. According to Schmiedeberg the differences in the several melanins depend on their mode of origin, inasmuch as these pigments represent the *final product of a long series of metamorphoses of albumin.* The albuminous bodies do not furnish the material for the building up of the final product (Schmiedeberg), but it is derived from sulphur-containing bodies formed by the cleavage of albumins, and from which certain carbon-containing groups have already been split off, so that there arise combinations which in propor-tion to their carbon-content are rich in sulphur; from these the melanins are formed.

Iron may be present in small amounts in melanotic pigment, but is usually absent and is not necessary to the production of melanin.

In the case of abundant formation, melanin may be excreted in the urine.

Lipochrome is the term applied to the coloring-matter of adipose tissue, corpora lutea, ganglion-cells (Rosin), of the greenish tumors known as chloromata (Krukenberg), and of the muscle cells of the heart in brown atrophy. It is greatly increased in the subcutaneous fatty tissues in pernicious anemia, giving a lemon-yellow color to the skin. Of the origin and nature of this pigment nothing definite is known.

Hæmofuscin (von Recklinghausen, Goebel) is the iron-free, yellowish granular pigment' found in smooth muscle of stomach and intestine. According to von Recklinghausen, this pigment is derived from the blood, but it has not been established that it is a hæmoglobin-derivative. The sulphur-content (Rosenfeld) makes it not unlikely that the hæmofuscin granules belong to the melanin group. It is a striking fact that when treated with " fat-stains " the hæmofuscin-granules are found to be fat-containing just as lipochrome stains as fat (Lubarsch).

According to *von Kölliker,* "the pigment of the hair and epidermis is derived from pigmented connective-tissue cells which lie just beneath the deepest layers of the epithelium of the hair-bulbs and of the rete, and send processes between the delicate cells of these layers. These processes divide into long fine ramifications which lie in the intercellular spaces and may even penetrate into the cells themselves, and in this way transfer their pigment to the latter." The pigment of the ganglion cells and of the cells of the retina arises, on the other hand, in the ectodermal cells themselves. *Riehl* and *Ehrmann* agree with *von Kölliker. Karg* observed that, following the transplantation of white skin on the surface of a leg-ulcer in a negro, the grafted portions became black in from twelve to fourteen weeks; and he concludes that, in the pigmentation of the epidermis, pigmented connective-tissue cells penetrate between the epithelial cells and convey pigment to the latter. Microscopic examination showed the presence of pigmented processes between the epithelial cells at a time when the latter had not yet became pigmented. *Von Wild* has shown that in melanosarcomata of the skin, pigmented connective-tissue cells may penetrate between the epithelial cells. Similar connective-tissue cells are found in the pigmented portions of the skin or mucous membranes in Addison's disease, usually, however, in certain areas only and not everywhere.

According to *von Fürth,* neither sulphur nor iron is necessary to the formation of melanin. The melanin-molecule contains, however, active atom-groups which enable it to combine with certain complexes rich in sulphur and iron. The investigations of *Bertrand, Biedermann, Schneider, von Fürth, Gessard,* and others make it probable *(von Fürth)* that the formation of melanotic pigment depends on the action of an oxidative ferment (tyrosinase), upon tyrosin or other hydroxylized substances of an aromatic nature. In the abundant formation of melanin in tumors, melanin or melanogen may be excreted in the urine, so that this at the time of discharge is black or gradually becomes black when exposed to the air and light.

According to *Spiegler,* the results of chemical investigation exclude the derivation of melanin from hæmatin. He also demonstrated the existence of a white chromogen which is the cause of white wool in sheep and of gray hairs.

In domesticated animals there occurs a peculiar **melanosis of the internal organs,** occasionally associated with melanosis of the subcutaneous tissue. The affected organs (heart, lungs, intestines, etc.) present in varying numbers grayish or black spots, looking like ink-spots, which are produced by the deposit of pigment in connective-tissue cells which otherwise appear normal.

Under the title of **ochronosis,** Virchow described a condition characterized by the deposition of brownish, blackish, or bluish black iron-free pigment, particularly in the cartilaginous structures of the body, but also in tendons, joint capsules, periosteum, and certain internal organs. The pigment stands in close relationship to melanin. Clinically, the pigmentation is most frequently noted in the cartilages of the external ear and of the nose, and in the sclerae and skin. Pathologically, the costal cartilages, the intervertebral discs, the articular surfaces of the large joints and the rings of the trachea are almost constantly pigmented. The epiglottis and laryngeal cartilages are usually less often and less deeply colored. The ligaments and tendons are involved in a considerable percentage of cases. Of the internal organs, the intima of the heart or the aorta is the most frequently pigmented. In cartilage, the deposition of the pigment takes place in the matrix, the capsule and cells being spared or only slightly affected, unless the cells themselves have been injured, and then pigment is apt to be deposited in large quantities. In a considerable proportion of cases, ochronosis is attended by destructive lesions in the larger joints, sometimes giving rise to symptoms comparable to those of arthritis deformans. In many instances ochronosis has been shown to follow the long continued application of dilute solutions of carbolic acid to chronic leg ulcers and the like (Poulsen: Ziegler's Beitr., 1910). The urine is characterized by the presence of

homogentisic acid (alkapton) which is a substance derived chemically from the destruction of proteins, particularly tyrosin and phenylalanine. Whether the long continued use of carbolic acid so influences protein metabolism as to cause the formation of homogentisic acid in the tissues and its liberation through the urine, has not been determined. Gross and Allard (Arch. f. exp. Path. u. Pharm., 1908) were unable to extract homogentisic acid from cartilage, but by placing pieces of fresh cartilage in dilute solutions for a period of from three to six weeks, they found the characteristic color changes of ochronosis.

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§ 70. **Hæmatogenous pigments** are those *whose origin from the coloring-matter of the blood may be demonstrated beyond doubt.* Such pigmentations are known as **hæmochromatoses.**

Extravasates of blood soon undergo changes which are visible to the naked eye. Extravasates in the skin become brown, then blue, green, and finally yellow. Small hæmorrhages into the tissues, as in the peritoneum, pleura, and lungs, may show for a long time as reddish-brown spots; in decomposing cadavers their color may be slate or black. Large hæmorrhages, as in the brain or lungs, assume after a time a rust-brown color, which later changes to ochre-yellow, y e l l o w, yellowish-brown, or brown. All these variations of color correspond to changes in the hæmoglobin and in the iron which it contains.
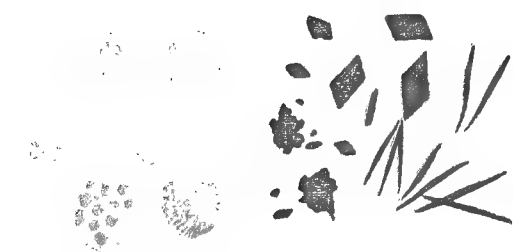
FIG. 96.—*A*, Cells containing amorphous blood-pigment; *a*, those with few large fragments of red blood-cells; *b*, *c*, those containing great numbers of small disintegration-products of red blood-cells; *B*, rhombic plates and needles of hæmatoidin. × 500.

Whenever **hæmorrhage** occurs in the tissues or into a cavity, a portion of the plasma and of the *red cells* may be taken up *unchanged* through the lymph-vessels. Another portion of the corpuscles loses its

hæmoglobin, the pale stroma of the cells remaining. The *escaped hæmoglobin diffuses* through the tissues, and from it are formed the different products which give rise to the changes of color in the neighborhood of the extravasate. A part of the absorbed hæmoglobin may be excreted as *urobilin* (*urobilinuria*); another part may be precipitated in the tissues in the form of granules or crystals. The latter are *yellowish-red or ruby-red rhombic plates and needles of hæmatoidin* (Fig. 96, B); and represent a frequent residuum of hæmorrhages. A portion of the diffused hæmoglobin may also be taken up by cells, the latter acquiring a diffuse yellowish pigmentation, or showing the presence of yellow and brown granules.

A third portion of the blood-corpuscles disintegrates at the site of the extravasation, and forms *yellow and brown granules and lumps.* The pigment which arises directly from the disintegration of red cor-
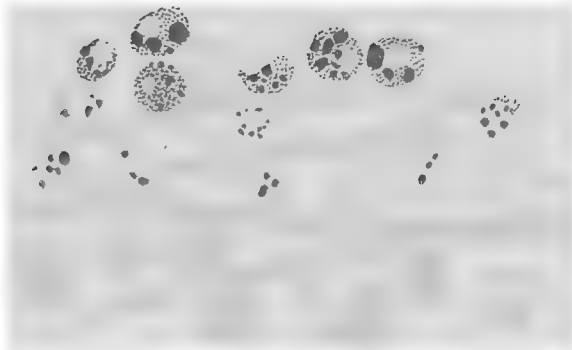
FIG. 97.—Cells containing hæmosiderin and hæmatoidin from an old hæmorrhagic focus in the brain. (Alcohol, Berlin-blue reaction.) *a,* Cells containing hæmosiderin; *b,* cells containing hæmatoidin; *c,* fat-granule cells which have become clear; *d,* newly formed connective tissue. × 300.

puscles, as well as the crystals and granules precipitated from dissolved hæmoglobin, are often taken up by cells, partly leucocytes and partly cells derived from proliferating tissue (Figs 96, A, and 97, *a, b*).

At the beginning of the disintegration of red corpuscles the coloring-matter present is hæmoglobin, but the yellow and rusty masses and granules which are found both in the cells and lying free, and which eventually become changed into darker pigment, are no longer hæmoglobin itself, but **derivatives of hæmoglobin**. According to their composition these may be divided into two groups, one iron-free, the other containing iron. The former is known as *hæmatoidin,* the latter as *hæmosiderin.*

Hæmatoidin (*identical with bilirubin*) is a ruby-red (Fig. 96, B) or reddish-yellow (Fig. 97, *b*) pigment occurring in crystalline form, or as granules, which may be amorphous, but often show a somewhat angular shape (Fig. 97, *b*), suggesting imperfect crystals. Hæmatoidin is soluble in chloroform, carbon disulphide, and ether; insoluble in water and alcohol. It appears to be formed when hæmoglobin is but slightly exposed to the action of living cells, as in the centre of large extravasates and in hæmorrhages into the body-cavities, for example, into the pelvis of the kidneys or the subdural space. It may be produced artificially by the introduction beneath the skin or into the peritoneal

cavity of capsules containing blood, so that the blood in the capsules is exposed to the action of tissue-fluids but not of cells.

The granules and crystals of hæmatoidin are found in the tissues free (Fig. 96, B), or enclosed in cells (Fig. 97, *b*). In the latter case they are taken up after they have been precipitated; occasionally it may happen that hæmatoidin in solution is taken up by fixed connective-tissue cells, for example, cartilage or fat-cells, and then precipitated in solid form.

Hæmosiderin, the derivative of the red blood-cells which contains *iron* in demonstrable quantity microscopically, is found in the tissues as yellow, orange, and brown granules and lumps which become darker in the course of time. They are for the greater part contained in cells, and in part are formed within the cells.

When treated with potassium ferrocyanide and dilute hydrochloric acid hæmosiderin becomes deep-blue through the formation of Berlin blue (ferric oxide salt of hydroferrocyanic acid) (Fig. 97, *a*). When treated with ammonium sulphide there is formed a black sulphide of iron.

Hæmosiderin appears to be formed particularly when the blood in an extravasate or in a thrombus is subjected to the action of living
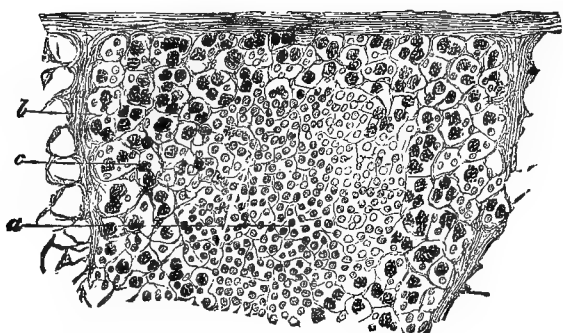
FIG. 98.—Accumulation of pigment-containing cells in the lymph-nodes after resorption of an extravasate of blood. (Müller's fluid, carmine.) *a*, Cortical node; *b*, lymph-sinus; *c*, cells containing pigment-granules. × 100.

cells; consequently it is seen more frequently in small extravasates and at the periphery of large ones. The formation of hæmosiderin may take place either in the cells or free in the tissue. The pigment enclosed in cells (sideroferous cells) may have been formed from disintegrated red corpuscles, or from dissolved hæmoglobin which has been absorbed by the cells. In favor of the latter mode of formation is the diffuse yellow color seen in both wandering and fixed cells, which becomes blue when the Berlin-blue reaction is applied. Further, when hæmoglobin is excreted through the kidneys, iron-containing pigment-granules form in the renal epithelium; and moreover fixed cells, as cartilage-cells, which could hardly be supposed to act as phagocytes and take up fragments of red cells, often contain granules of hæmosiderin, even when lying outside the immediate neighborhood of the extravasate.

The free pigment and pigmented cells cause distinct pigmentation of the extravasate and its neighborhood. The pigmented cells pass into the lymph-vessels and *metastasis of pigment* takes place, as a result of which pigment is found in the lymph-vessels and in the lymph-nodes, (Fig. 98). Later it may be taken up by the fixed tissue-cells. In time the hæmosiderin is destroyed and disappears. The view that hæmosiderin is changed into melanin, is not supported by facts. The brownish-black granules in the lungs, which have been explained as due to such a change,

consist of one or several minute particles of carbon surrounded by a coating of hæmosiderin.

If hæmosiderin is brought into contact with hydrogen sulphide it becomes black; and as the result of such reaction there may be produced in the cadaver black and green spots or a more diffuse discoloration, known as **pseudomelanosis.** It is observed most often in the intestine, peritoneum, and in suppurating wounds, since in these regions hydrogen sulphide is more likely to be formed by putrefaction.

Ziegler uses the term hæmochromatosis in its strict sense, namely, to indicate a condition in which the associated pigments are derived from hæmoglobin. The term hæmochromatosis, however, is widely, if somewhat loosely, employed to designate a condition which many regard as a distinct morbid entity and which is characterized by the deposition not only of an iron-containing pigment, but of one which is free from iron. Neither pigment is traceable to hæmoglobin. Moreover, the condition is attended by increase in the pigmentation of those tissues which normally contain pigment. Hæmochromatosis is probably best interpreted as a metabolic process implicating different tissues, and characterized by the deposition in them of pigments formed as a result of disturbances in the chromogenic structures of the proteid molecule. According to this view, the iron-containing pigment in hæmochromatosis, hæmosiderin, is derived from iron-containing proteids native to the pigmented tissues; certainly there is no dissemination of pigment by metastasis. The non-iron-containing pigment in hæmochromatosis is hæmofucsin. In the majority of all cases of hæmochromatosis, the skin presents a diffuse bronze discoloration and diabetes is present (diabète bronzé of the French). The cause of the diabetes is unknown. While in most cases the pancreas is pigmented, the islands of *Langerhans* are unchanged, so that the diabetes cannot be ascribed to anatomical changes in these structures. In most cases of hæmochromatosis the liver is cirrhotic. Hæmochromatosis is not common. It occurs oftenest in males. Of sixty-three cases collected by *Sprunt* (Arch. Int. Med., 1911) only one was in a female. In Bellevue Hospital, eight cases were observed among 6,000 autopsies. Two of these were associated with cirrhosis and primary carcinoma of the liver, and still another with myelomatosis. Hæmochromatosis as an attendant phenomenon in cirrhosis of the liver with primary carcinoma is exceedingly rare, but has also been observed by *Runte* (Inaug. Disser. Wurzburg, 1901) and by *Loehlein* (Ziegler's Beitr., 1907) and *Winternitz* (Virch. Archiv., 1913). In hæmochromatosis the organs most frequently involved are the liver, pancreas, spleen, lymph nodes and heart muscle. In this connection it is interesting to recall that *Kretz*, in twenty-six cases of atrophic cirrhosis of the liver, was able to demonstrate iron-containing pigment in fourteen, the remaining organs being free from pigment. At Bellevue Hospital we have been able to confirm this observation in a number of instances.

§ 71. **When large numbers of red blood-cells break down in the circulating blood,** dissolved hæmoglobin or methæmoglobin may pass into the plasma, and fragments of red cells may be carried in the circulation. Such destruction of red cells occurs to a marked degree in poisoning with arsenic, toluylendiamin, potassium chlorate, and morels; to a lesser degree in other conditions, such as infections, malaria, in pernicious anæmia, and in overheating of the body. The passage of hæmoglobin or methæmoglobin into the blood-plasma leads to the condition of *hæmoglobinæmia;* the plasma is colored red. When the amount of dissolved hæmoglobin in the blood is large, a portion may be excreted through the kidneys, giving rise to *hæmoglobinuria* or *methæmoglobinuria,* in which conditions the urine may present a bloody appearance, or vary from clear brownish-red to dark reddish-black. This occurs particularly in the first-named poisons, but occasionally after the action of other injurious influences, for example, exposure to cold (periodical hæmoglobinuria).

When *formed products* arise from the disintegration of red cells, such as corpuscular fragments after extensive burns, they collect in the

capillaries of the liver, spleen, lymph-nodes, and bone-marrow, and to a less extent in other organs; and are sooner or later taken up by phagocytic cells.

As the result of increased supply of hæmoglobin to the liver the functional activity of this organ is increased, so that the *amount of pigment in the bile may be greater than normal;* under certain conditions oxyhæmoglobin may appear in the bile (Stern). When the blood-destruction is great, the liver may not be able to dispose of all the pigment brought to it; and in consequence **derivatives of hæmoglobin are deposited** in the liver and other organs, or **excreted** by the kidneys. In the former event there may arise more or less extensive **hæmochromatosis** of different organs, the cells of which show an ochre-yellow or brown color. The derivatives of hæmoglobin deposited in this way are partly *iron free pigments* and partly *hæmosiderin.*
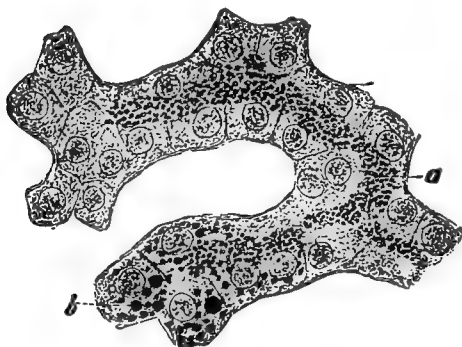
FIG. 99.—Infiltration of the cells of the liver-rods with yellow hæmosiderin granules, from a case of pernicious anæmia. (O·mic acid.) *a,* Hæmosiderin; *b,* cells in a state of fatty degeneration. × 250.
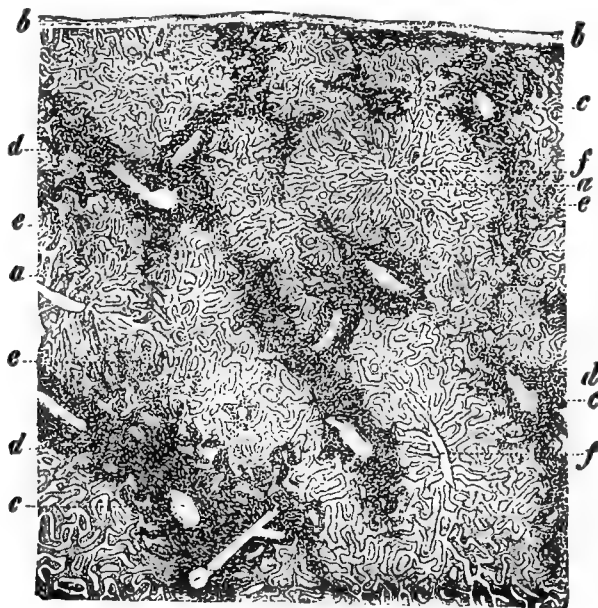
FIG. 100.—Hæmochromatosis of the liver. (Alcohol, carmine.) *a,* Acini; *b,* peritoneum; *c,* branches of the portal vein; *d,* infiltrated periportal connective tissue; *e,* pigment lying within the liver-acini; *f,* central veins. × 20.

The **deposits of iron-containing pigment** in the liver appear in the form of yellow granules and lumps, which are enclosed in leucocytes

lying in the capillaries. The deposits are found also in the form of granules in the endothelial cells of the capillaries (to which the stellate cells of Kupffer belong), and in the liver-cells (Fig. 99, *a*). In many diseases, for example, pernicious anæmia, the cells contain so much iron pigment that the liver takes on a characteristic yellowish-brown color.

The iron-pigment which is carried to the *spleen* is deposited chiefly in the free cells of the pulp; but granules are also found in the fixed cells. In the *lymph-nodes* the iron granules are found in the free cells
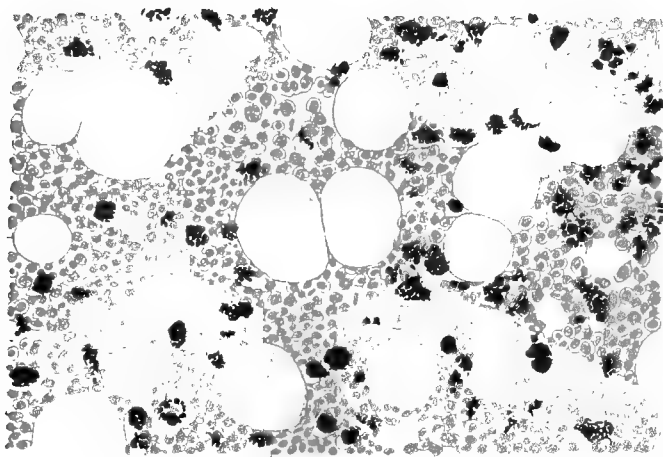
FIG. 101.—Hæmosiderin deposit in the bone-marrow (mixed fatty and lymphoid marrow), in icterus. (Alcohol, carmine, Berlin-blue reaction.) × 300.

of the lymph-channels. In the *bone-marrow* retained hæmosiderin (Fig. 101) is found in cells lying in the capillaries, and partly in the endothelium and marrow-cells; the number of iron-containing cells may be marked.

In the *kidneys* the hæmosiderin granules are most abundant in the epithelium of the convoluted tubules (Fig. 102, *a*), but are also found in the lumina of the tubules (*b*), in the epithelium of Bowman's capsule (*e*), and in the endothelium of the capillaries. In marked deposits the kidney may show signs of pigmentation to the naked eye.

The hæmosiderin found in different tissues is brought to them in the form of small lumps or granules contained in leucocytes. On the other hand, another part is precipitated in the cells from substances brought to them in solution. Since the cells (liver-cells, kidney epithelium, endothelium of the blood-vessels, and the cells of the lymph-nodes, bone-marrow, and spleen) not infrequently show a diffuse blue color after the iron-test has been applied, the iron must be diffused through the cell-protoplasm, and converted later into granular form. It is also possible that the diffuse coloration may arise from solution of iron in the cells. According to the observations of different investigators, it appears that besides the colored deposits of pigment, colorless granules or an iron-albuminate may be present in the cells. This theory is supported by the fact that more pigment granules are visible after the iron reaction has been applied, than could be seen before.

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The **deposit of iron-free pigments,** *hæmatoidin* or *bilirubin* is not of frequent occurrence in hæmochromatosis, but occasionally yellow granules which do not give the iron reaction are found in the organs named above; and it may, therefore, be assumed that the pigment in part may be constantly free from iron.

By certain writers the *mottled pigmentation of the skin* which develops in *chronic arsenic poisoning,* and which is due to the deposit of small yellowish-brown granules in the corium and epidermis is classed with the hæmochromatoses and is referred to the degenerative influence of arsenic on the bone-marrow and blood.
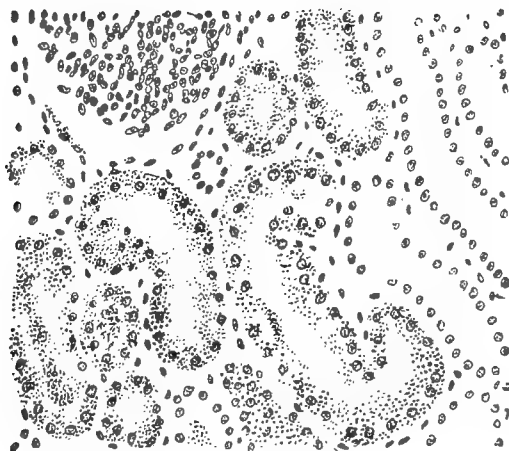
FIG. 102.—Hæmatogenous deposits of iron in the kidney in pernicious malaria (contracted in Bagamayo). (Alcohol, carmine, Berlin-blue reaction.) *a,* Convoluted tubules, whose epithelial cells contain iron granules and are stained diffusely blue; *b,* iron-granules in the lumen of the tubules; *c,* straight tubules; *d,* glomerulus; *e,* epithelium of the capsule, containing iron-granules. × 150.

It should be noted, however, that the pigment does not give the iron reaction, and, moreover, that pigment in epithelium that is derived from hæmoglobin is not permanent; and that no increased destruction of red blood-cells occurs in habitues of arsenic (*Muir*).

In **malaria** *two pigments* are formed as a result of the destruction of red cells by the parasite. One of these is formed by the malarial plasmodium itself, is contained in the parasite, is black, and gives no iron reaction. Its nature is not known.

The second pigment is hæmosiderin, which passes into the blood-plasma as the result of the destruction of red blood-cells, and is deposited in the liver, spleen, and bone-marrow. In marked destruction of blood there may occur siderosis of the kidneys (Fig. 102), and excretion of iron in the urine.

Froin, Nonne and others have described a condition attended by yellowish discoloration of the spinal fluid (*xanthochromia*) in which the protein content is increased to such an extent that, when the fluid is removed, it coagulates spontaneously. The condition may be encountered in compression of the spinal cord and its meninges from any cause which leads to the formation of a cul-de-sac distal to the site of compression. In these circumstances, *Hanes* (Amer. Jour. Med. Sc., 1916) is of the opinion that the yellowish color of the fluid is due to transudation of blood serum owing to interference with the circulation at the site of compression. Pleocytosis may or may not be present, depending on whether the meninges are inflamed. Xanthochromia of the spinal fluid is to be sharply distinguished from staining by hæmoglobin derivatives (erythrochromia), which may occur in a number of conditions attended by hæmorrhage into the cerebro-spinal fluid.

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(Hæmochromatosis; Iron Absorption; Deposit and Excretion.)

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§ 72. **Icterus** or **jaundice** is a pathological discoloration of tissues due to bile-pigment. It is a symptom which occurs in numerous diseases of the liver, and is often encountered as a fugitive process in the first few days of life (*icterus neonatorum*).

The pigment which characterizes icterus is apparent during life in the skin, conjunctiva, and urine; in the cadaver the internal organs — serous membranes, lungs, kidneys, liver, subcutaneous and intermuscular tissues, blood-plasma, clots in vessels, etc.— may show icteric coloration. In recent cases the icteric color is yellow; in long-standing cases the skin takes on an olive-green or dirty grayish-green color, while similar colorations occur in the internal organs, particularly in the liver, and often in the kidneys.

Icterus results from the entrance of bile-pigment (bilirubin) into the blood and fluids of the body. The urine excreted contains elements of bile, particularly the pigments. As the result of disease in the biliary passages or liver the outflow of bile is hindered, and the bile is then taken into the lymphatics and blood-vessels of the liver. Such damming back of bile may be caused by narrowing or closure of the large bile-ducts through scar-tissue, through gall-stones wedged in the lumen, or tumors developing in the bile ducts or compressing them; or through inflammatory processes or tumors of the liver which compress or obliterate the smaller ducts, and in this way hinder the outflow of bile.

In the case of stasis of bile in the liver-lobules the intercellular bile-capillaries become dilated and filled with bile-thrombi (Fig. 103, *a, b*). The dilatation also affects the blind side branches extending toward the capillaries, and these may be broken through, so that the bile eventually gains entrance into the lymph-channels and blood. Further, the bile-pigment is heaped up in the liver-cells themselves (*c*), and the endothelium of the blood-capillaries (*d, d₁, e*) is stained.

When bile-pigment obtains entrance to the blood, the *tissues of the body become gradually permeated* and acquire an icteric color. If phagocytes containing granules of bilirubin are present in the circulating blood, they may accumulate here and there, particularly in the spleen and bone-marrow. After a time the bile-pigment held in solution in the tissue-lymph may become precipitated as *solid particles,* chiefly in granular form, but sometimes as crystals in the fixed and wandering cells of the connective tissue, in the liver-cells, and in the renal epithelium. The crystals are in the form of rhombic plates and needles, similar to those of hæmatoidin (Fig. 96). In severe cases of icterus many of the tissue-cells contain pigment, and, as a result of metastasis of cells containing pigment, accumulations of the latter in the lymph-nodes may occur.

In kidneys in which bile-pigment is being excreted deposits of bilirubin occur, particularly in the epithelium of the urinary tubules (Fig. 104, *a, d*), which in consequence may become desquamated. If, as the result of damage to the secreting cells through the excretion of bile-pigment, there are formed, as usually is the case, hyaline casts — that is, hyaline coagula in the albumin-containing urine in the tubules — these likewise become colored (Fig. 104, *b, c*).

Associated with the bilirubin in icterus there is sometimes a *deposit*
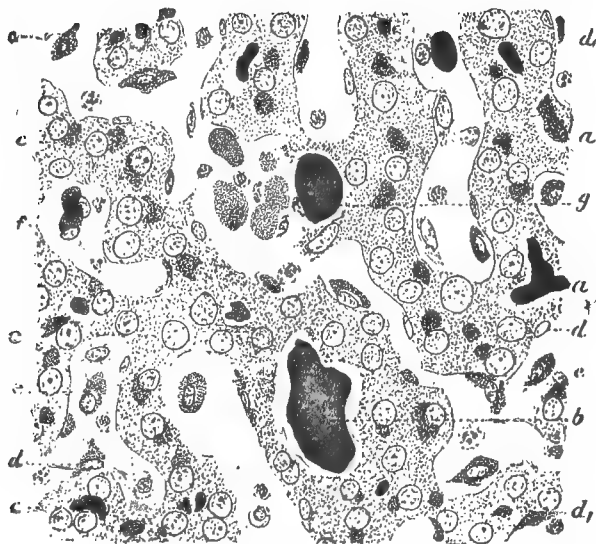
FIG. 103.—Obstructive icterus of the liver, due to compression of the ductus choledochus by a cancer of the gall-bladder. (Sublimate, alum-carmine.) *a,* Intra-acinous bile-capillaries, moderately dilated and filled with bile; *b,* widely dilated intra-acinous bile-capillary, containing large mass of pigment; *c,* bile-pigment in the liver-cells *d, d₁,* endothelium stained with bile-pigment; *e,* desquamated endothelium stained with bile-pigment; *f,* pigment mass surrounded by cells; *g,* rupture of the pigment contained in a bile-capillary into a blood-capillary, with bile-stained cells in the neighborhood. × 365.

of hæmosiaerin which may become so abundant in the bone-marrow (Fig. 101), spleen, and lymph-nodes, and occasionally in the liver, that discoloration of the organs named is dependent in part on iron-pigment.

When *increased destruction of red blood-cells* takes place in the blood-vessels, hæmatoidin or bilirubin, in addition to hæmosiderin, is formed in different parts of the body (see § 71); but the formation of bilirubin outside of the liver is slight and is not sufficient to cause extensive icteric coloration of the tissue, so that, according to one view, *pure hæmatogenous jaundice does not occur.* The liver is the great elaborator of bilirubin, and in cases of increased destruction of blood-cells the liver-function is increased and there is increased production and excretion of bile-pigment. *Icterus due to increased destruction of blood-cells* can occur only when there are present in the liver such changes as cause *passage of bile into the blood.*

The question as to whether there is a hæmatogenous as well as a hepatogenous variety of jaundice has long been an object of discussion, and remains unsettled at the present time, in spite of numerous experimental investigations directed toward

its solution. Since, as a matter of fact, bilirubin may be formed in different kinds of tissue from extravasated blood, the occurrence of hæmatogenous icterus would *a priori* appear probable. Experimental investigations as to the results of the destruction of red cells in the circulating blood, particularly through the action of arsenic, toluylendiamin, and potassium chlorate, have shown that the derivatives of blood-pigment which are formed in the tissues and there retained for a long time are essentially iron-containing pigments (hæmosiderin), while the production of bilirubin is practically confined to the liver, which for the time being secretes an increased amount of richly pigmented bile.

According to the investigations of *Minkowski* and *Naunyn,* the urine of geese and ducks after removal of the liver contains no bile-pigment—a fact which would
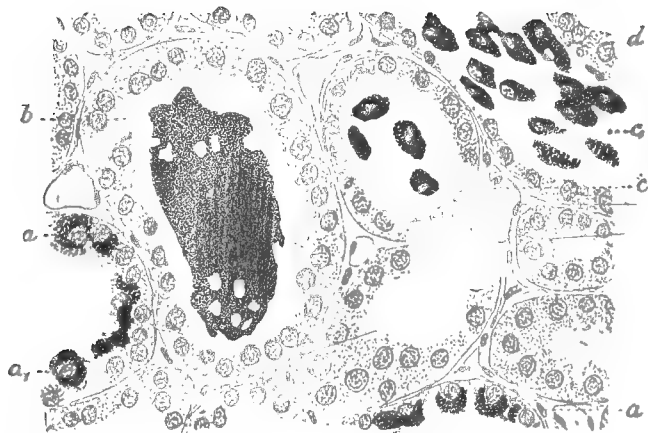
FIG. 104.—Icterus of the kidney in obstructive jaundice. (Sublimate, carmine.) *a,* Tubular epithelium containing yellowish-brown granules; *b,* large casts stained yellowish-green; *c,* cast containing pigmented cells; *d,* desquamated epithelium containing bile-pigment granules. × 200.

indicate that the transformation of blood-pigment into bile-pigment is ordinarily confined to the liver. The inhalation of arseniuretted hydrogen for a few minutes is sufficient to produce in geese an intense polycholia and hæmaturia, the urine containing hæmoglobin in solution, disintegrating red cells and biliverdin. If the liver from such a goose be removed, the biliverdin quickly disappears from the urine, and no trace of bile-pigment can be demonstrated in the blood. It is therefore evident that in arsenic poisoning the formation of bile-pigment is confined to the liver, in which organ leucocytes enclosing iron-containing fragments of broken-down red cells are found to be present.

In so far as it is possible to judge from experimental investigations which have been made up to the present time, pure hæmatogenous jaundice does not appear to be improbable. The mere fact of the occurrence of jaundice after intoxications, inhalation of ether and chloroform, transfusion of blood, snake-bite, septicæmia, typhoid fever, yellow fever, paroxysmal hæmoglobinuria, etc., cannot be taken as proof of the existence of hæmatogenous jaundice. There is, indeed, in these conditions increased destruction of red blood-cells; but jaundice, if it occurs, may be due to the fact that a portion of bile-pigment, which is produced in excess, has found its way into the blood. According, however, to *Whipple* and *Hooper,* the intravenous injection of hæmoglobin into dogs with the liver excluded is followed by the excretion of bile pigment in the urine and jaundice of the fat tissues. (Jour. of Exp. Med., 1913.) Moreover, there are well-defined varieties of hæmolytic icterus in which the destruction of red cells takes place in the spleen and in which removal of the spleen is almost invariably followed by disappearance of the jaundice.

According to *von Kupffer* and *Pfeiffer,* the bile-capillaries terminate in intracellular secretory vacuoles; from these, according to *Nauwerck, Stroebe,* and *Browicz,* delicate intracellular secretory canaliculi are given off, forming a network around the nucleus. *Schäfer* describes small canaliculi within the liver-cell com-

municating with the blood-capillaries. *Arnold* opposes the view that any preformed system of canals exists in the liver cells.

In the icterus occurring so frequently in the new-born (*Schmorl*) there occurs both a diffuse and a scattered yellowish coloration of the brain limited to the neighborhood of the nuclei, while in later life the brain, even after long-continued icterus, remains free from pigment. With the nuclear icterus there are also found ganglion-cells stained with bile.

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(*Icterus.*)

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§ 73. **Pigmentation of the tissues through materials introduced from without** occurs when substances possessing a color of their own gain entrance and are able to remain for some time without suffering changes. The number of such substances is large, and the manner of
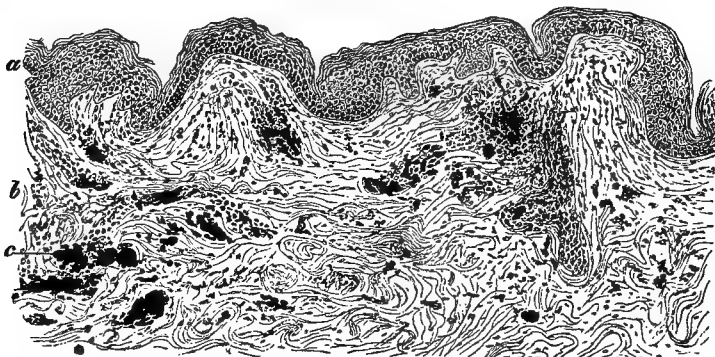
Fig. 105.—Deposit of cinnabar in tattooed skin. (Alcohol, alum-carmine.) *a*, Epithelium; *b*, corium; *c*, cinnabar. × 80.

entrance varied. The most *common avenues of entrance* are the *lungs, wounds,* and *intestinal tract.* The most familiar pigmentation through wounds is *tattooing of the skin,* which is frequently practiced by individuals civilized as well as uncivilized.

The method of tattooing colored figures, etc., consists in the introduction of insoluble granular pigments, such as carbon, india-ink, cinnabar, sepia, burnt sienna, ultramarine, chromate of lead, etc., into slight wounds of the skin. The pigments are rubbed into the wounds, whence they penetrate and infiltrate the tissue in their immediate neighborhood. A portion of the pigment remains in the *corium* (Fig. 105, *c*); another portion is carried to the lymph nodes, which become pigmented.

The lungs and their lymph nodes may become intensely pigmented through the inhalation of *colored dust,* such as coal-dust, soot, iron-dust, etc. Through the inhalation of coal-dust the lungs may become black.

When coal-dust is taken into the lungs in the respired air a portion of the pigment is carried to the peribronchial lymph nodes, which may become black. When the deposit is abundant the lymph nodes may undergo softening and give off pigment into the lymph-stream. If the nodes are situated in the neighborhood of a vein, the pigment-deposit and the softening may involve the vein-wall, so that particles of coal-dust may pass into the blood-stream, and be carried to other organs, the spleen, liver, and bone-marrow (see § 21).

From the *intestine* only soluble substances are absorbed, and permanent pigmentation can therefore occur only when these are precipitated in the tissue as solid particles which retain a distinguishing color. The most frequent of such pigmentations is that known as *argyria*, which is due to the long-continued use of silver preparations, whether taken by mouth or applied to mucous membranes, e.g., the nose, or to chronic ulcerative lesions of the skin. In argyria the skin may show only a slight bluish tinge, but in more pronounced cases the silvery discoloration lends a ghastly appearance. The internal organs may present more or less pigmentation. The silver is deposited in the ground-substance of the tissue in the form of fine granules, more especially in the glomeruli, and the connective tissue of the medullary pyramids (Fig. 106, *b*), the intima of the great vessels, adventitia of the smaller ones, in the neighborhood of mucous glands, the papillæ of the skin, connective tissue of the intestinal villi, and in the choroid plexus of the lateral ventricles. Deposits may also occur in the serous membranes, but the epithelial tissues, the brain, and the cerebral vessels escape. Extensive deposits of silver in the medullary portion of the kidneys may lead to the formation of hyaline connective tissue and to calcification.

FIG. 106.—Deposits of silver in the pyramidal portion of a rabbit's kidney, after seven months' administration of silver salts (experiment by von Kahlden.) (Alcohol, hæmatoxylin.) *a*, Epithelium of the collecting tubes; *b*, connective tissue with brown silver granules. × 500.

Iron taken into the body in excessive amounts, may be deposited in the bone-marrow, spleen, and lymph-nodes; but the pigmentation thus produced is rarely visible to the naked eye. In *lead-poisoning* there may be seen a grayish-black discoloration of the gums, due to the deposit of sulphide of lead in the connective tissue produced through the action of hydrogen sulphide on lead which is present in solution in the mucous membrane.

A variety of exogenous pigmentation has recently been described under the title of carotinæmia, and is characterized by the presence in the blood and urine

of pigments derived from diet rich in carotin — carrots, spinach, the yolk of eggs, oranges, etc. The condition is evidenced by a peculiar orange-yellow tint of the skin which simulates jaundice, but is easily differentiated from the latter by lack of discoloration of the conjunctivæ. (Palmer and Eckles, Journ. Biol. Chem., 1914; Palmer, Ibd., 1916; Hess and Myers, Carotinæmia, Journ. Amer. Med. Assn., 1919.)

XV. The Pathological Absence of Pigment.

§ 74. **Absence of pigment** occurs as a congenital condition, and is termed **albinism or leucopathia congenita.** In such cases the absence of pigment may extend over the entire body (*albinismus universalis, albinos*) ; in other cases it is restricted to certain portions of the skin (*albinismus partialis*). In those parts of the skin which are destitute of pigment the hairs likewise contain no pigment, and appear white or yellowish-white (*poliosis* or *leucotrichia congenita universalis, et circumscripta*). In universal albinism the pigment of the retina, choroid, and iris may be wanting, so that the choroid, from the blood which it contains, appears red, and the iris, according to the angle of observation and the degree of illumination, appears bluish-white or red. On microscopic examination no pigmented cells are to be found.

Fig. 107.—Vitiligo endemica (after a photograph received from Professor Münch.)

A second form of albinism is known as **vitiligo or leucopathia acquisita.** This occurs later in life, either as a sequel to certain diseases (scarlet fever, typhus, recurrent fever), or as a symptom of an epidemic disease of unknown etiology (vitiligo endemica), or finally without any recognizable cause. The formation of white spots, in which the hairs are also white (*leucotrichia acquisita circumscripta*), takes place usually symmetrically, and may extend over the greater part of the body (Fig. 107). The white areas are surrounded by a border of deeply pigmented skin; this suggests that with disappearance of pigment at one point the pigment is transferred to adjacent parts. The loss of color in the hairs (as in old age) begins in the root, no more pigment being transferred from the hair-papilla to the bulb. Finally the pigment-cells of the papilla disappear altogether.

A third form of loss of pigment is associated with traumatic or infectious *inflammations* of the skin, particularly in syphilis and leprosy; this condition is known as **leucoderma.**

In scars of the skin which remain white, the newly formed tissue replacing the defect does not possess the power of producing pigment. Not infrequently such a scar may be surrounded by a pigmented border.

In mild forms of inflammation, in which the tissue of the skin suffers no loss (syphilis), the disappearance of color may immediately follow the inflammation, or not until later, in which case there may occasionally occur a preceding stage of increased pigmentation. According to Ehrmann the lack of pigment in such cases is to be explained either by the fact that no chromatophores are present in the corium to furnish pigment to the epithelium, or the changed epithelium is not able to take up the pigment from the latter when present. The pigment which still remains in the cutis may then be absorbed.

According to *Münch,* vitiligo is of common occurrence in Turkestan, and is considered by the natives (Sarts) to be contagious, so that they isolate the affected individuals and confine them with lepers in enclosed courts. It is probable that in the literature vitiligo endemica has been many times confused with lepra maculosa, and has been described under the designation "white leprosy of the Jews."

XVI. The Formation of Cysts.

§ 75. A **cyst** is a circumscribed cavity which is shut off from the surrounding tissues by a connective-tissue membrane or by tissue of a more complex structure, and possessing contents differing in nature from the capsule. Cysts may occur in any tissue. When composed of but a single chamber, the cyst is called a *simple cyst;* when divided into a number of compartments, it is known as a *multilocular cyst.*

The most common form is the so-called **retention-cyst,** *which arises from the accumulation of secretions in preëxisting spaces which are lined with epithelium or endothelium.*

In **glands provided with ducts,** retention-cysts are formed as the result of obstruction of the duct, provided secreting epithelium exists behind the point of obstruction. Such cysts are of frequent occurrence in the sebaceous glands, hair follicles, uterine glands, mucous glands of the intestinal tract, tubules of the epididymis (Fig. 108, *c*), urinary tubules; less frequent in the biliary passages, in the breast, pancreas, in the glands of the mouth, etc. **Larger open canals,** such as the ureters, vermiform

FIG. 108.—Section of the testicle and epididymis, with multiple cysts in the head of the epididymis. *a,* Testis; *b,* epididymis; *c,* multilocular cysts. Slightly reduced.

appendix, and Fallopian tubes, may also undergo cystic dilatation as the result of the collection of secretions. Obstruction of a duct may be due to accumulation of secretion, to the formation of adhesions, cicatricial obliteration, compression, or constriction of its lumen.

Closed glandular cavities and tubes, such as the follicles of the thyroid and the glandular tubes of the parovarium, may become cystic when their walls produce an abnormal amount of secretion. Likewise, the **remains of fœtal passages and clefts,** for example, remains of the branchial clefts, urachus, Müller's ducts, etc., may become cystic.

Small cysts such as those developing in mucous glands, vary in size from a millet seed to that of a pea. Larger cysts, such as occur in the liver and ovaries, may attain the size of a fist and even larger.

The **contents of cysts** depend on the nature of the tissue in which they are formed. Thus cysts of sebaceous glands and hair-follicles contain a pultaceous, white, or grayish-white, more rarely brown, mass, which consists of squamous cells in various stages of disintegration, fat-globules and cholesterin. The cysts occurring in mucous glands contain a fluid which is either clear, or white and cloudy, as the result of the presence of cellular elements. Hæmorrhage into a cyst gives a red or brown color to the contents. When great numbers of cells are present in cyst-contents, the whole may become converted into a semi-solid fatty mass, and eventually undergo calcification. Cysts of the thyroid and kidneys contain colloid masses, or a clear though occasionally cloudy fluid.

Retention-cysts lined with endothelium may develop from lymph-vessels, lymph-spaces, bursæ, and tendon-sheaths. Here also the content of the cyst is dependent on its place and mode of origin.

As retention-cysts tend to increase in size the stretching of the cyst-wall would ultimately lead to a defect in the continuity of the wall if no *new formation of tissue* took place. Cyst formation is not purely a degenerative process; new formation of tissue takes place in the epithelial or endothelial lining of the cyst, and the connective-tissue elements of the wall also increase, so that in spite of the stretching, the wall becomes no thinner, and may even increase in thickness. Moreover, **cyst formation is often associated with pathological overgrowth of glandular tissue,** and in this way constitutes a secondary change in hyperplastic or tumor growths. It is, therefore, sometimes impossible to draw a sharp line between the simple cystic dilatations of preëxisting gland-canals and gland-spaces, and those tumors, the **cystomata,** which are characterized by cyst formation (see Cystoma).

A second form of cyst is the **degeneration-cyst,** which arises through partial disintegration and liquefaction of tissue. Cysts formed in this manner occur in the brain, hypertrophic thyroids, and in tumors. They may contain a clear or cloudy, or at times hæmorrhagic exudate.

A third form of cyst results from the formation of a **connective-tissue capsule** around **foreign bodies,** which have found entrance to the tissues, for example, about a bullet; or about **necrotic areas,** or **hæmorrhagic extravasates.**

A fourth variety of cyst is formed by **parasites** which pass through a cystic stage in the course of their development in the body, and are likewise surrounded by a *connective-tissue capsule.*

CHAPTER VI.

Hypertrophy and Regeneration. Results of Tissue-Transplantation. Metaplasia.

I. General Considerations.

§ 76. In a broad sense, **hypertrophy** is *increase in the size of a tissue or organ, due either to increase in the size or in the number of the individual elements,* in such a way that the structure of the hypertrophic tissue is like that of the normal, or at least does not differ essentially from it.

In a limited sense *hypertrophy is increase in size due to enlargement of the individual elements alone; enlargement due to increase in the number of the individual elements* being designated *hyperplasia.*

If the enlargement affects the entire body, for example, if a newly born child weighs 5-8 kgm., or if an individual should reach the height of 180-200 cm., the condition is called **giant growth.** When the enlargement affects individual parts of the body, for example, the entire head or one-half of it, or one extremity, or the vulva, it is called **partial giant growth.** Hypertrophic growths of the skin and subcutaneous tissues, leading to disfigurement suggesting the appearance of the pachydermata, are known as **elephantiasis**(Figs. 109, 110).

In giant growth all the elements are uniformly enlarged. In elephantiasis the connective tissue of the skin

FIG. 109.—Elephantiasis femorum neuromatosa.

and subcutaneous structures is especially likely to become increased; nevertheless the structure of these growths may vary greatly. In one case all the connective-tissue elements may be uniformly increased, in another case only individual elements; for example, the connective tissue of the nerves, blood- or lymph-vessels. It is therefore possible to distinguish *different forms of elephantiasis* according to the structure of the hypertrophic part; *elephantiasis neuromatosa, angiomatosa, lymphangiectatica, lipomatosa, fibrosa,* etc.

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Hypertrophy of the horny layer of the epidermis attended by the formation of plates, scales, or even spines, is designated **ichthyosis** because of a fancied resemblance to the external covering of the fish. 'The condition is usually inherited and its cause is unknown (ichthyosis congenita) Fig. 111, *c.*

In other cases during the first years of life, localized thickenings of the horny layer develop, consisting of small scales or plates, or larger ones, giving the skin a rough and checkered appearance. The corium and the papillæ are usually not involved in the ichthyosis; but occasionally the papillary bodies may be hypertrophic, thus increasing the rough and nodular appearance of the surface (*ichthyosis hystrix*). When the excessive cornification is sharply limited to areas of small size, there are formed circumscribed warts with rough epithelial covering, known as *ichthyotic warts.* In rare cases there may be developed a more extensive horny layer over the hypertrophic papillæ, whose scales are arranged at right angles to the surface of the skin; these occasionally attain such size that they are called **cutaneous horns** (Figs. 112, 113).

The excessive and coarse development of hair over those parts of the body where only downy hair, or no hair at all, should be found is known as **hypertrichosis.** Abnormal hairiness may cover a large or small area, and depends either on persistence and abnormal development of the lanugo (hypertrichosis lanuginosa fœtalis) (Fig. 114), or on pathological development of the secondary hairs. Excessive growth of the nails leads to the condition known as *hyperonychia,* which is often followed by the claw-like deformity designated *onychogryphosis.* It is to be noted, however, that pathological overgrowths of the nails are usually acquired.

Fig. 110.—Elephantiasis cruris lymphangiectatica.

Next to the enlargements associated with general or partial giantism the **bones** most frequently undergo hypertrophy corresponding to elephantiasis of the skin. The head is usually affected, the bones of which may undergo enlargement (Fig. 115), leading to a deformity in which the head comes to resemble that of a lion, hence the name **leontiasis ossea.** Further, there often develop on the skull or other bones circumscribed bony growths known as **exostoses.**

It cannot always be stated to what extent hypertrophy of the tissue is to be attributed to congenital predisposiion, inasmuch as many extrinsic

influences are able to produce proliferations of tissue similar to those due to intrinsic causes. For example, cutaneous horns and elephantiasis-like thickenings of the skin may develop as the result of inflammation.
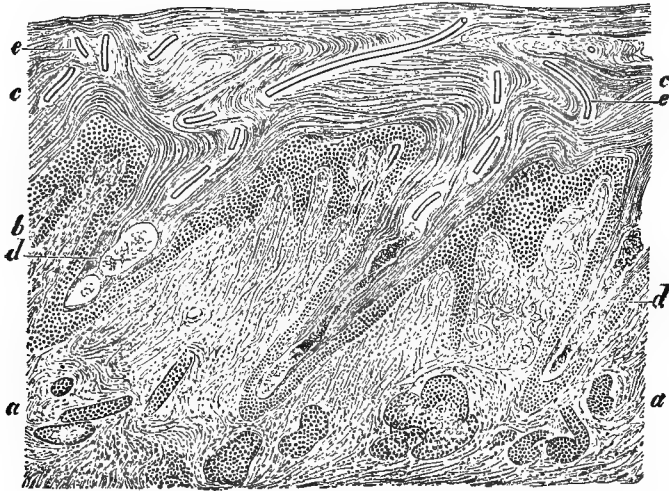
Fig. 111.—Ichthyosis congenita. Section through the skin of the trunk of the body (alcohol, picrocarmine.) *a,* Corium, with glands; *b,* papillary body, with rete Malpighii; *c,* hypertrophic horny layer of the epidermis; *d,* dilated hair-follicles, lined with horny epithelium; *e,* hairs. × 40.

In general, the early appearance of a hypertrophic growth and the absence of any obvious etiological factor, speak for the congenital nature of the condition. The fact that later influences may apparently cause the growth does not preclude the existence of a congenital predisposition. Thus the excessive bony growths of the head above mentioned may follow trauma or acute inflammations. External influences may therefore be the exciting but not the primary cause of the change.

Not infrequently the tendency to excessive growth may show itself in *premature development of certain organs, the structure remaining normal.* The sexual organs are most frequently affected. Girls, even in the first years of life, may show development of breasts and external genitals and growth of hair corresponding to that of the sexually ripe woman; and menstruation may be established at this early period.
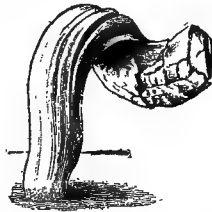
Fig. 112.—Cornu cutaneum, from back of hand. (Natural size.)
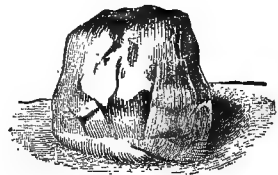
Fig. 113.—Cornu cutaneum, from arm. (Natural size.)

The size of the body as well as of its separate parts and organs shows considerable variation within physiological limits, according to the race, family, and individual. The variation in the relation of the size of single parts and organs to that of the entire body is less marked.

The average height of the body in well-built individuals is, according to Vierordt ("Daten u. Tabellen für Med.," Jena, 1893), as follows: Men 172 cm., women 160 cm.; of the new-born, males 47.4 cm., females 46.75 cm. The average body-weight in Europe is for men about 65 kgm., that of women about 55 kgm., that of the new-born about 3,250 gm.

The average weight of the internal organs is as follows, the figures in parentheses being for the new-born: Brain 1,397 (385) gm., heart 304 (24) gm., lungs 1,172 (58) gm., liver 1,612 (118) gm., spleen 201 (11.1) gm., right kidney 131, left kidney 150 gm., both kidneys 299 (23.6) gm., testicles 48 (0.8) gm., muscles 29,880 (625) gm., skeleton

Fig. 114.—Head of a hairy individual, a woman. (After Hebra.)

Fig. 115.—Leontiasis ossea, occurring in a boy affected with general giant-growth. (Observed by Buhl.)

11,560 (445) gm. Expressed in percentages of body-weight the figures for adults and new-born are (the latter in parentheses): Heart 0.52 (0.89), kidneys 0.48 (0.88), lungs 2.01 (2.16), stomach and intestines 2.34 (2.53), spleen 0.346 (0.41), liver 2.77 (4.30), brain 2.37 (14.34), adrenals 0.014 (0.31), thymus 0.0086 (0.54), skeleton 15.35 (16.17), muscles 43.09 (23.4).

Literature.

(Tissue-Hypertrophy of Congenital Origin.)

Arnheim: Congen. halbseitige Hypertrophie. Virch. Arch., 154 Bd., 1898 (Lit.).
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§ 77. **Hypertrophies due to external causes** arise in response to increase in the activity of the tissue, to diminished use, defective retrograde change, or to prolonged or frequently repeated mechanical, chemical, and infectious irritations. Removal of pressure may sometimes be followed by localized hypertrophy.

Hypertrophy from overwork is most frequently observed in *muscles* and *glands,* but may also occur in other tissues. If the *heart* is called on to do an extra amount of work as the result of diseased conditions of the valves, aorta or kidneys, and if such conditions exist for some

time, that part of the heart-muscle on which the extra work falls suffers more or less pronounced hypertrophy, so that as a result the mass of the heart may reach several times that of the normal.

In similar manner *the unstriped muscle of the bladder, ureters, uterus, intestine, and blood-vessels* may become hypertrophic from persistent increase in activity.

As the result of increase of strain from whatever cause *bones* may become thickened, and the trabeculæ of the medullary portion increase in size.

Of the *glands* the *kidneys,* and *liver* in particular are able to change their size according to functional demands, and may present marked hypertrophy. Should one kidney be destroyed, the other may become so enlarged that it reaches approximately the same weight that the two together originally possessed. Likewise the liver after destruction of a part of its parenchyma may make good its loss by hypertrophy of the remainder. Since in this way compensation for the defect and restoration of function are brought about, such increase is d e s i g n a t e d **compensatory hypertrophy.** The same term may be applied to muscle-hypertrophy, if through it functional disturbances are compensated. Compensatory hypertrophy is said to occur in similar circumstances in adrenal tissue. In other glands, such as the salivary glands, ovaries, testicles, and mammae, compensatory hypertrophy either does not occur at all, or takes place only dur-

Fig. 116.—(Bellevue Hospital.) Showing the peculiar hypertrophy and malformation of the lower extremities in Paget's disease, so-called osteitis deformans.

ing the period of development. The loss of an ovary or testis in adult life can hardly result in increased activity and hypertrophy of the remaining organ. Extirpation of the larger part of the thyroid gland is not followed by pronounced hypertrophy of the remaining portion; on the other hand, the hypophysis undergoes enlargement which must be regarded as compensatory. In the *lungs,* increase in the activity of one portion after the loss of another results usually in over-distention which eventually may lead to atrophy. On the other hand, if during embryonic life defective development of one lung takes place, the other lung may undergo compensatory growth, which in case of total agenesia of one lung may reach a pronounced degree. For the other

organs the general principle may be applied that compensatory hypertrophy more nearly approaches perfection the younger the individual. In the brain compensatory growth of one part after the loss of another is possible only during the early stages of development.

Hypertrophy from lessened use occurs in tissues which are normally subject to attrition from constant use. For example, diminished desquamation of the horny layer of the epidermis leads to pathological thickening. If, as the result of the destruction of an opposing tooth or an oblique position, the incisor teeth in rodents are not worn down by use, they may grow into long, curved tusks. **Hypertrophy due to defective retrograde change** occurs in organs which after a definite period of physiological growth undergo diminution in size. For example, the uterus after pregnancy may remain abnormally large as the result of failure of involution. The thymus gland, which should begin to atrophy after the tenth year of life, may persist for a much longer period. In bones **lessening of pressure** may be followed by hypertrophy. In idiots whose brains are deficient in size there is often hyperostosis of the inner surface of the base of the skull (Chiari), and unilateral hyperostosis of the skull is sometimes associated with corresponding hypoplasia of the brain.

Frequently repeated or protracted mechanical, thermal, chemical, or infectious irritations give rise to proliferative processes leading to hypertrophies, which because of their etiology and course must be regarded as chronic inflammations; such formations are placed under the head of **inflammatory hypertrophy.** They are characterized often by the fact that in the enlargement of the organ, not all of its parts are equally involved; certain elements, usually the connective tissue, occasionally the epithelium, undergo hypertrophy to such a degree that the *structure of the organ* (skin, gland, etc.) *is no longer typical.*

If the skin is frequently subjected to irritation and pressure, for example, the toes through an ill-fitting boot, there may arise thickening of the horny layer of the epidermis, known as *callus* or *corn* (*clavus*). Prolonged irritation of the skin in the neighborhood of the genital openings, caused by gonorrhœal discharges, may be followed by elongation and branching of the papillæ with thickening of the epithelium, leading to the formation of warty, cauliflower-like growths known as *venereal warts* or *condylomata acuminata.* Chronic inflammations of the corium and subcutaneous tissue, due to infection or to animal parasites (*Filaria Bancrofti*), not infrequently give rise to fibrous hypertrophies known as *elephantiasis.* Such hypertrophies may attain extraordinary proportions. In similar manner there may occur in the bones, as the result of chronic infectious processes (syphilis, for example), extensive hypertrophies characterized by increased formation of bone-substance.

In the majority of cases those tissue-hypertrophies which appear during life as acquired formations, the *causa efficiens* may be recognized with more or less certainty but there are also cases in which, at the present time, this is either impossible or possible to a limited extent. For example, there are *enlargements of the spleen, and of lymphadenoid tissues* in various localities which are of the nature of hypertrophies, whose causes we are unable to recognize. Imperfect, also, is our knowledge of the etiology of the *enlargements of the extremities,* resembling partial giant-growth, which have been described as *ostéoarthropathie hypertrophiante* (Marie).

In Germany the designation acromegaly is applied to all forms of enlargement of the ends of the extremities that lead to paw-shaped deformity of the hands and gigantesque appearance of the feet, while *Marie* attempts to draw a line between acromegaly and ostéoarthropathie hypertrophiante. He holds that in acromegaly the hands and feet are not deformed, but are symmetrically enlarged, the thickening and broadening diminishing toward the tips of the extremities, so that the terminal phalanges of the fingers and toes are but slightly thickened, while, on the other hand, in ostéoarthropathie hypertrophiante the terminal phalanges are enlarged to resemble drumsticks, and the articular ends of the bones are irregularly thickened. In the first affection the lower jaw is lengthened, in the latter it is thickened. *Marie* believes that ostéoarthropathie hypertrophiante is a sequel of inflammatory affections of the lungs and pleuræ, and designates the condition ostéoarthropathie
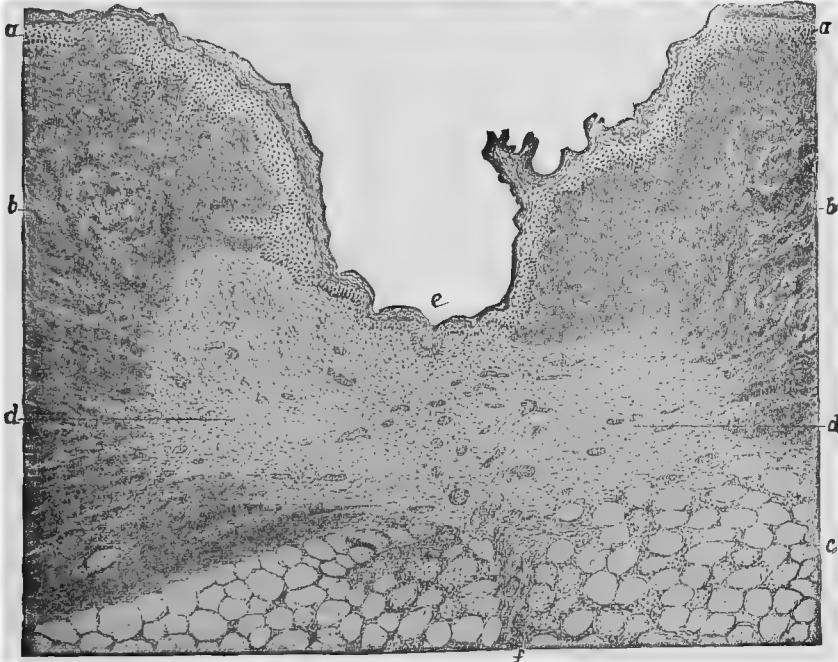
FIG. 117.—The skin-portion of a laparotomy wound sixteen days old (Müller's fluid, Van Gieson's). *a*, Epithelium; *b*, corium; *c*, subcutaneous adipose tissue; *d*, scar in corium; *e*, new epithelium; *f*, scar in adipose tissue. × 38.

hypertrophiante pneumique, and holds that the connection between these processes is to be found in the taking up into the body-fluids of poisonous products from the inflammatory foci in the lungs, so that the affection of the bones is to be regarded as an infectious toxic hypertrophic inflammation.

The association of acromegaly with tumors of the hypophysis of different kinds has been definitely determined, but the character of the tumors in some cases would indicate increase of function, in other cases diminution or loss.

The cause of the nodular hypertrophy of the thyroid gland, occurring so frequently in many regions, is unknown.

§ 78. **Regeneration** is that *process through which tissues which have been destroyed are restored.* It is *the result of new-formation of cells, which arise through the division of preëxisting cells.*

Regeneration presupposes that the **injured tissue is capable of proliferation,** and is a phenomenon which in all cases is dependent on **extrinsic causes.** In the fully developed organism, *each tissue can pro-*

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duce only new tissue of its own or a closely related kind. The **specificity of tissues** is so decided that epithelial cells can never give rise to connective tissue, and connective tissue can never produce epithelium. Ectodermal cells cannot produce intestinal epithelium; kidney epithelium can produce only cells having the character of kidney epithelium, but never liver-cells or those of mucous glands, or connective tissue. Muscle-tissue can arise only from muscle-cells. Nerves and neuroglia can never arise from connective tissue. Only cells which are closely related can arise from the same parent-tissue. Thus the periosteum can produce
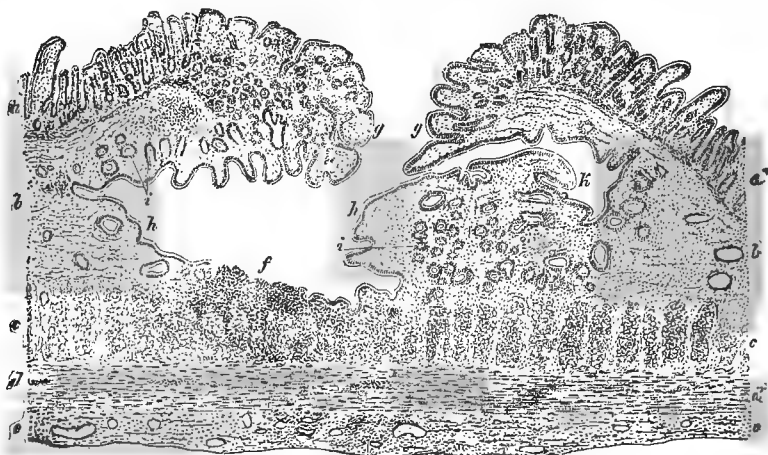
FIG. 118.—Healing ulcer of the small intestine, with formation of new gland-tubes in the proliferating submucosa (Müller's fluid, hæmatoxylin). *a*, Mucosa; *b*, submucosa; *c*, *d*, muscularis; *e*, serosa; *f*, remains of the floor of the ulcer not yet covered over with epithelium; *g*, overhanging edge of the ulcer; *h*, portion of floor of ulcer covered with epithelium; *i*, newly formed glands in the submucosa; *k*, deep crypt lined with epithelium. × 18.

ordinary connective tissue, cartilage, or bone — that is, tissues which are modifications of the same connective-tissue.

In *tissue defects in which only single cells are lost* (for example, in the loss of single connective-tissue cells), or in more extensive destruction of cells *without interruption in the continuity of the connective tissue of the blood-vessels* (as the loss of localized areas of surface epithelium, or a group of gland cells or of pulmonary epithelium), **complete regeneration,** *restitutio ad integrum,* may take place, and the tissue be restored to a condition corresponding to that existing before the injury. *After injuries in which the continuity of the mesodermal supporting tissue is broken,* with or without associated injury to tissues of ento- and ectodermal origin, **regeneration is incomplete;** at the point of injury tissue is formed which departs more or less from the normal in both structure and function. In general this is newly formed *connective tissue,* designated **scar** (Fig. 117, *d*) or **cicatricial tissue.** Defects of the skeleton are replaced by scar-tissue which arises from the periosteum and endosteum, and by virtue of the peculiar properties of these tissues new bone develops in the scar, the structure coming eventually to resemble that of normal bone.

In many instances *cicatricial tissue* consists purely of *vascularized connective tissue* (Fig. 117, *d*). Scars bordering on ectodermal or entodermal tissue may become covered by epithelium (Fig. 117, *e*). Occasionally

the structure of cicatricial tissue may be modified, in that *specific tissue-formations grow into it secondarily* or are *preserved in it as remains of preëxisting structures.* The first process occurs most frequently in scars of the mucous membrane of the intestine (Fig. 118), and of glands in the neighborhood of their excretory ducts. In defects of mucous membranes which are replaced by scars formed through proliferation of connective tissue (Fig. 118, *b, f*), the surface is first covered with epithelium (*g, h, k*), later epithelial ingrowths develop which bear the character of tubular glands (*i*). Gland-ducts (bile-ducts, ducts of the salivary glands) may grow into developing scar-tissue, and form new tubes or solid cords of cells. Such new-formation of ducts may occur not only in the neighborhood of traumatic injuries, but also in the course of inflammations of the glands in question.

On the other hand, regeneration of gland-tissue proper in the neighborhood of scars is wanting in the majority of instances, (liver, kidneys, testicles, ovaries, thyroid, mammary glands). Only in the salivary glands does the development of new ducts lead to the formation of gland-lobules.

In muscle-scars (Fig. 119) it is said that new muscle-fibres (*d*) grow from the ends of the old ones (*a*), so that the scar becomes gradually replaced by muscle.

The remains of specific tissue-elements in the area of cicatrization may be observed in both muscles and glands, especially at the periphery of traumatic injuries and anæmic necroses (Fig. 120), and in inflammatory foci. The glandular remnants in the scar usually present an atrophic appearance, (Fig. 120, *b*), but islands of normal tissue (*d*) may also be enclosed, and it is possible that these may even undergo compensatory growth.

In inflammatory processes in
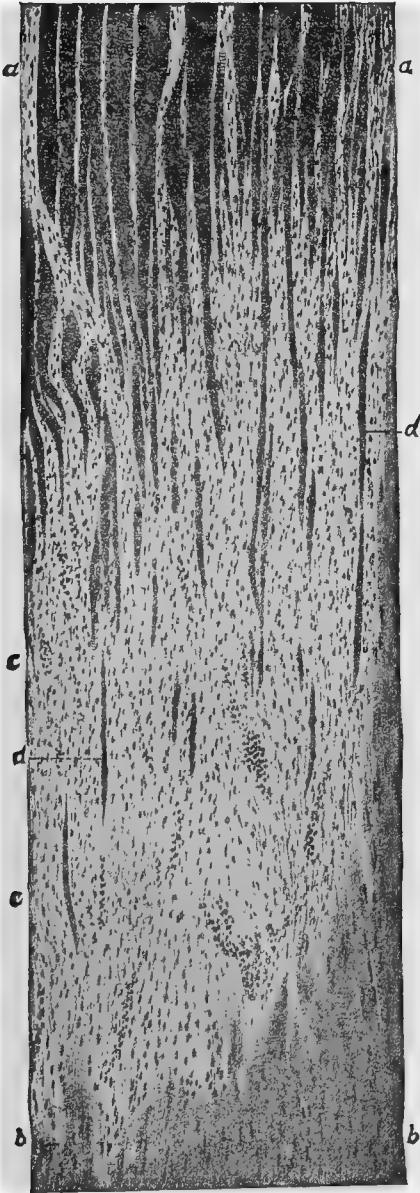
FIG. 119.—Scar of muscle and tendon, thirty-two days old (Flemming's solution, Van Gieson's). *a*, Old muscle; *b*, tendon; *c*, scar; *d*, newly formed muscle-fibres. × 100.

glandular organs characterized by   destruction of perenchyma, and by the regeneration and overgrowth of connective tissue, there are often seen atrophic remains of gland-tissue, and between these, islands of un-injured gland-tissue that have undergone hypertrophy.

The **mass of the scar** is rarely equal to the mass of the tissue lost; there persists after the loss of considerable tissue a more or less marked **defect**. In circumscribed areas of skin, mucous membranes, glands, brain, etc., such a defect gives rise to *cicatricial depression*. Numerous
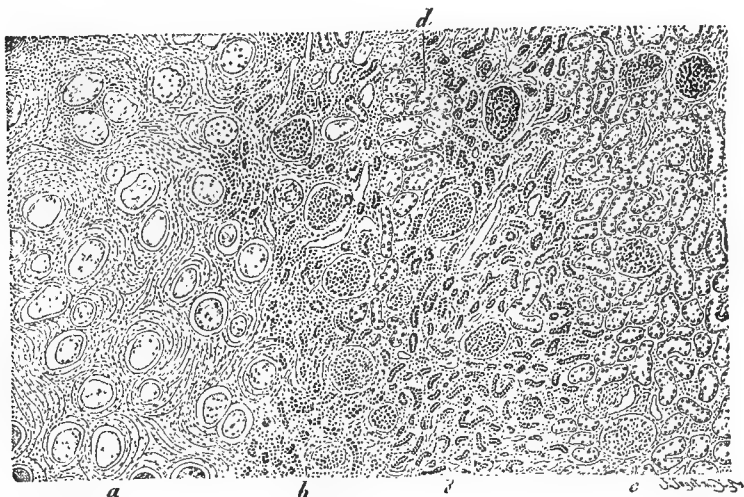
FIG. 120.—Peripheral zone of an embolic scar (Müller's fluid, hæmatoxylin and eosin). *a*, Scar showing obliterated glomeruli, but no tubules; *b*, indurated tissue with atrophic tubules, the glomeruli being preserved; *c*, normal cortical tissue; *d*, island of normal tubules in the scar. × 30.

cicatricial depressions in an organ may occasion atrophy characterized by irregular configuration of the surface.

The loss of tissue *en masse,* for example, a toe, is in man *never replaced*. Such defects are closed by scar-tissue which on superficial parts of the body becomes covered with epithelium.

In man and other mammals, the **regenerative capacity of tissues** is rela-tively slight. This depends on the fact that human and other mammalian cells are so highly differentiated that they are unable to revert to such a low embryonal state as to produce different forms of tissue. In spite of this limitation the regen-erative powers are sufficient to restore continuity and to preserve the external covering of the body. If as the result of local loss of tissue, the life of the organ-ism be endangered through inability of the tissues to restore the lost part, there exists in certain organs (liver, kidneys) the power of compensating for such loss through hypertrophy of remaining normal tissue.

In the lower animals the power of regeneration is greater than in mammals; and further is greater in the earlier stages of ontogenesis, so that, in many animals (tritons, ascidians, echinoderms, teleosts), the first two or even the first four segmentation cells still possess the power of forming an entire embryo.. Insects possess during the larval state marked power of regeneration, which later is lost.

In protozoa each animal may quickly supplement itself through division. In the fresh-water polypi fragments of the body may develop into the entire animal. The angle-worm is able to replace either tail or head end when these are cut off. The wood-louse can replace its feet and antennæ, the snail its tentacles and anterior extremity, crabs and crayfish their claws and legs. Salamanders are able to restore legs, eyes, and tails, and lizards and slow-worms their tails, when these are broken

off. In frogs, snakes, and fishes, on the other hand, the power of regeneration diminishes as the scale of animal life is ascended, yet this does not happen equally in the case of all animals, and animals closely related to each other may show different capacities for regeneration. Further, in the same animal the regenerative power is not the same in all organs; for example, in tritons the regenerative capacity of the internal organs is slight. Moreover, the power to form a new portion of the body, as a tail or extremity, for example, does not prove that all the tissues of the portion of the body in question possess an especial capacity for proliferation. In crayfish and crabs regeneration of the claws and legs takes place only from certain places; in injuries occurring at other points, the new extremity is thrown off only at that place where a new-formation is possible. In tritons, fractures of the bones heal slowly, although they are able to reproduce their extremities.

§ 79. The **cause of cell-proliferation** underlying hyperplastic and regenerative changes in tissue varies according to the conditions under which proliferation occurs.

The *"stimulus"* may consist in the **removal of hindrances to growth**, since experience teaches that the majority of the cells of the body possess the power to divide, even those cells in which the process of division has apparently been in abeyance for long periods of time. There may also be present a **formative stimulus, which increases both the reproductive capacity and the tendency to reproduction.** Such a stimulus may act independently — that is, without the removal of influences inhibiting growth — this is assumed in cases in which after the loss of a portion of an organ the remaining portion (liver, kidney) undergoes compensatory hypertrophy, although, even in these circumstances, it is difficult to exclude changes in the equilibrium of cells brought about mechanically or otherwise, and affecting the relationship of cells to one another or the elements of individual cells.

The stimuli which are able to excite growth and cell division are known in part only. They appear to be identical with the stimuli which excite or increase functional and nutritive activity. In muscles, hypertrophy is brought about by increased contraction following nervous excitation. Liver and kidney tissue undergo hypertrophy when, as a result of loss of a large area, the remaining portions are obliged to do an increased amount of work.

Whether other formative stimuli exist cannot be stated with certainty. Increased supply of blood and nutrition, believed by many to act as a formative stimulus, is not in itself sufficient to excite regeneration of cells; it gives rise merely to increased deposit of fat. Increase of the temperature of tissues may hasten the process of cell division and thus promote tissue proliferation; but it is doubtful if it can directly excite proliferation in resting tissues. The action of heat followed by proliferation (for example, in the skin) produces local changes of a degenerative nature, so that the occurrence of proliferation may be explained as due to the removal of influences that otherwise inhibit growth.

There are chemically active substances that are capable of exciting proliferation. Thus, slight irritation of the skin produced by iodine is capable of causing proliferation without preceding detectable degenerative changes, although it is probable that degenerative changes in these circumstances do occur, but are of such nature as readily to be overlooked. In addition, such substances as Sudan III, scarlet-red, ether, indol, etc., when injected in the tissues, provoke a remarkable growth of epithelium and other tissues that, in certain instances, may resemble a neoplasm. It has been suggested that the effect of such substances is due to solution

of the lipoid membrane which is supposed to envelop each cell, thus exposing the nucleus to influences from which it otherwise is protected.

Finally, it must be noted that even the hypertrophied muscles and glands, following increased activity, cannot be regarded as the direct result of nervous or chemical stimuli, but we must assume that, with the increased labor, there is excessive consumption of cell elements which excites regenerative processes, the latter leading not only to restoration of the elements that are lost, but also to enlargement of the cell mass, together with the formation of new cells.

§ 80. The **division of the nucleus and cell-body,** on which the formation of new tissue depends, may occur through direct **segmenta-**
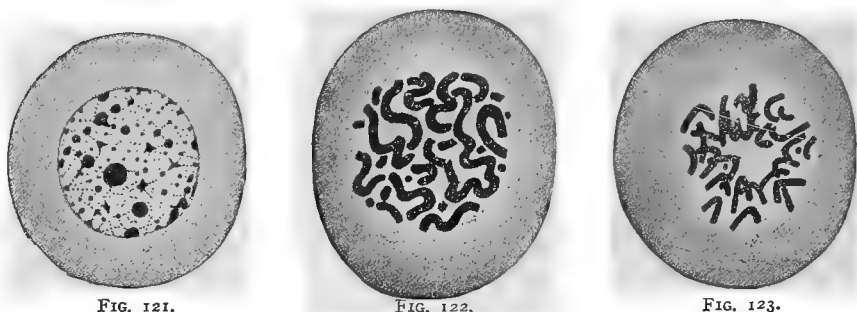
FIG. 121.   FIG. 122.   FIG. 123.

FIG. 121.—Enlarged nucleus.   Increase in the chromatin framework.
FIG. 122.—Thick, open skein, with segmentation of the threads into chromosomes; the nucleolus and nuclear membrane have disappeared.
FIG. 123.—Grouping of the completed chromosomes into a star-or wreath-form.

tion, that is, through transverse constriction of the elongated nucleus and protoplasm without increase or characteristic grouping or movement of the chromatin elements of the nucleus. It appears, however, that direct division of the nucleus leads to the production of cells which are able to form new tissue only when it is connected with that form of cell-division known as **karyokinesis** or **karyomitosis** or **indirect segmentation,** which is characterized by *increase of the* **nuclein** or **chromatin,** *and a definite cycle of changes of form and movements on the part of the latter.*

Karyomitosis follows a typical course in the normal growth of tissue, but deviations are frequently seen in pathological formations.

A **resting nucleus** consists of the *nuclear membrane,* and the *nuclear contents.*   The latter are composed of a colorless *nuclear fluid* and the *nuclear substance.*   To the nuclear substance belong the *nucleolus* and *scattered granules and threads* which form a framework staining with nuclear stains.

When the nucleus undergoes **division,** there occurs, first, *increase of the chromatin,* and the chromatin *framework* becomes more distinct (Fig. 121).   The nuclear substance then forms a *close skein,* which, with disappearance of the nuclear membrane and the nucleolus, becomes changed into an *open skein* with thick threads (Fig. 122), whose individual components divide themselves into *nuclear segments* or *chromosomes* (in man these number eighteen) (Figs. 122, 123).

These segments then group themselves in the equatorial plane of the nucleus with their angles directed toward the centre, forming, when

viewed from the polar aspect, a wreath-like (Fig. 123), and later a star-like figure, lying in the equatorial plane, that has been designated the mother-star (Figs. 124, 125), or equatorial plate.

Sooner or later *two poles* become visible in the so-called polar field — that is, two extremely small spherules, which are known as the *polar* or *central corpuscles* or *centrosomes*. At first these lie close together, but later separate and act as centres about which the nuclear elements group
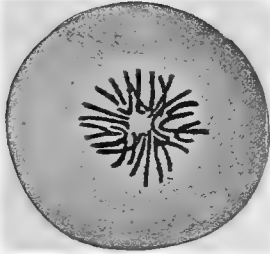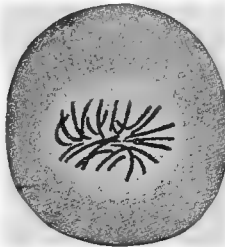
FIG. 124.   FIG. 125.   FIG. 126.
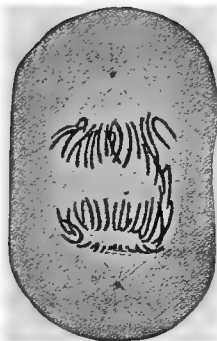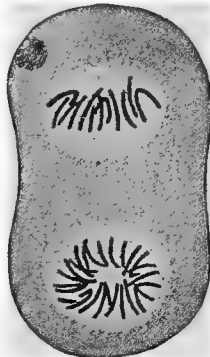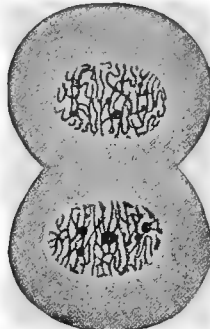
FIG. 127.   FIG. 128.   FIG. 129.

FIG. 124.—Completely developed mother-star; polar view.

FIG. 125.—Mother-star; equatorial view.

FIG. 126.—Stage of metakinesis. Single loops visible, their angles pointed toward the pole; delicate spindle-figure within the nucleus.

FIG. 127.—Daughter-star; side view (nucleus barrel-shaped); spindle-figure in the nucleus and the radial arrangement of protoplasm are visible.

FIG. 128.—Daughter-stars separated; the upper one presenting polar aspect, the lower one a side view.

FIG. 129.—Daughter-skein with fine threads (above), and with lattice-work (below). Completed division of the protoplasm.

themselves. Between these there is formed the *nuclear spindle* (Figs. 126, 127) which consists of fine threads which do not stain with nuclear stains, and converge in the polar corpuscles. In the neighborhood of the polar corpuscles themselves the granules of the protoplasm present a radial arrangement, giving rise to figures (Fig. 127) which are known as *ray-figures, stars,* or *attraction-spheres*. In the succeeding stage of division of the nucleus, a movement takes place among the chromosomes leading to the formation of loops, whose angles are directed toward the pole. Later the loops divide in halves which, following the direction of the spindle-fibres, move toward the poles and form two stars (Figs. 126–

128) which are known as *daughter stars*. From the star-figures the daughter-star passes successively through the thick-skein and then the fine-skein stage (Fig. 129, upper part) which finally changes into the nuclear *framework* (Fig. 129, lower part). During the later stages of the process a new nuclear membrane is formed.

In the stages of the segmented skein, or later as may be seen in the large nucleated cells of cold-blooded animals, there occurs *longitudinal*
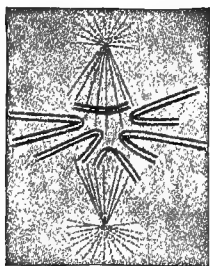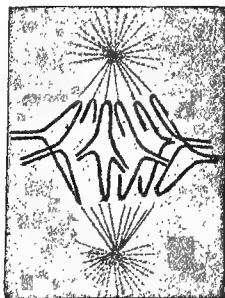
FIG. 130.   FIG. 131.

FIG. 130.—Mother-star, with chromosomes split longitudinally. (After Rabl.)
FIG. 131.—Metakinesis. The halves of the chromosomes are separating from each other and turning toward the poles. (After Rabl.)

splitting of the *chromosomes* (Fig. 130). In the change of position of the chromosomes known as *metakinesis* the halves of the split threads separate from each other (Fig. 131) so that each daughter-star receives half of the substance of each chromosome.

Division of the cell-protoplasm usually takes place at the time the daughter-star changes into the ordinary nuclear condition, and consists in constriction and separation of the protoplasm (Fig. 129). It is probable that a complicated interrelationship exists between the nucleus and cell-protoplasm; but the nucleus is to be regarded as *the more highly organized substance, as the centre of cellular potentiality. The nuclei are also the bearers of heredity,* while the protoplasm governs the relations of the cell with the outer world.

Variations from the typical karyokinesis may consist in the occurrence of *pluripolar division* in place of the bipolar, so that two to six or more nuclear spindles and a correspondingly increased number of equatorial plates (Fig. 132, *a*) may be formed. Further, in place of the

FIG. 132.—*a*, Pluripolar division-figure; *b*, *c*, asymmetrical division-figures.

simple mother-star there may be formed a complicated figure out of the chromatin loops, from which several daughter-stars may be evolved. Not infrequently there occur *asymmetrical divisions of the nucleus* (Fig. 132, *b*, *c*), particularly in tumors, but also in regenerative or inflammatory new-formations of tissue.

There are also divisions of the nucleus which are characterized by *abnormal size, abnormal richness in chromatin,* and *manifold variations*

of form. As types of such division are the large oval or bean-shaped (Fig. 133), knobbed or convoluted, lobulated and branched (Fig. 134), wreath-shaped, linked, basket-shaped (Fig. 135) nuclei, and other forms. Finally, there are occasionally found in the cells more or less extensive, indistinctly-outlined heaps of granular and lumpy chromatin (Fig. 136).
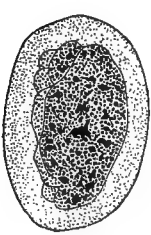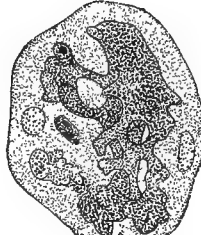
FIG. 133.   FIG. 134.   FIG. 135.   FIG. 136
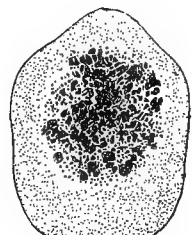
FIG. 133.—Cell with oval, slightly knobbed giant-nucleus, rich in chromatin.
FIG. 134.—Cell with lobulated giant-nucleus.
FIG. 135.—Cell with basket-shaped giant-nucleus.
FIG. 136.—Cell with large masses of chromatin.   All these cells from a sarcoma of bone.
(*Stroebe, Beiträge von Ziegler,* VII.)

Such nuclear forms are found in the cells of the bone-marrow, and in tumors which arise from the bone-marrow or periosteum, but have been observed elsewhere, particularly in certain sarcomata. Certain of these forms are due to contraction, and have nothing to do with cell-division. In other cases these changes of size and form precede division of the nucleus through constriction, sometimes with, sometimes without increase of the chromatin.   Arnold has designated division by constriction with increase of the chromatin as *indirect fragmentation,* that without such increase as *direct fragmentation.*   Indirect fragmentation differs from mitosis or indirect segmentation in the lack of orderly arrangement of the chromatin in threads,

FIG. 137.—Proliferating adipose tissue from the subcutaneous panniculus, twenty-six days after cauterization with trichloracetic acid (formalin, hæmatoxylin). *a,* Multinuclear fat-cells; *b,* proliferating connective tissue. × 300.

and in the irregularity with which the separation of portions of chromatin results in new nuclei.

Variations in the cell-protoplasm occur, either as *total failure of the protoplasm to divide* after division of the nucleus has taken place, or as *delayed division.*   These phenomena are observed in both mitotic and amitotic division of the nucleus, and lead to the formation of **multinuclear giant-cells** (Fig. 137).

Cells of the bone-marrow and of tumors arising from the bones show this phenomenon with special frequency. Proliferating fat-cells likewise form multinuclear giant-cells (Fig. 137, *a*). Besides this form of multinuclear giant-cell there also occur those formed by the *confluence of cells,* which are known as **syncytial giant-cells.** (Compare the sections on Inflammation and Tuberculosis).

Literature.

(*Cells and Cell-division.*)

For a complete exposition, see Wilson: "The Cell in Development and Inheritance," New York, 1897.

II. The Processes of Hyperplasia and Regeneration in Various Tissues.

§ 81. The morphological changes in the **regeneration and hyperplasia of epithelium** are relatively simple. The karyomitoses (Fig. 138, *a–d*) show for the greater part a typical course. The division of the protoplasm takes place either in the later stages of nuclear division or follows shortly thereafter. Giant-cells may arise through failure of the protoplasm to divide.

Epithelium arises only from epithelium. It is to be noted, however, that under certain conditions regenerating epithelium may change its character. This may occur, for example, in cicatrization of ulcers in the trachea. Defects in the ciliated columnar epithelium are repaired by low columnar or flat cells which later become changed into high columnar cells.

Small losses of superficial epithelium are replaced through regenerative growth of neighboring cells (Fig. 139, *d*, *d₁*, *d₂*), The epithelium bordering on the defect pushes over the denuded surface and begins to proliferate. The
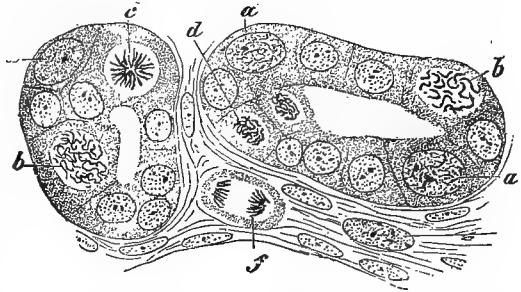
Fig. 138.—Regenerative proliferation of the epithelium of bile-ducts, in the neighborhood of a wound of the liver five days old (Flemming's solution, safranin). *a,* Enlarged nucleus of epithelial cell, with increase of chromatin; *b,* epithelial cell with mother-skein; *c,* epithelial cell with mother-star; *d,* epithelial cell with daughter-skein; *f,* connective-tissue cell with daughter-star. × 400.

division of the nucleus and cell-protoplasm takes place not only on the edge of the defect, but at some distance from it. In the intestine the loss of superficial epithelium is made good by proliferation of the epithelial cells in the crypts of Lieberkühn. Likewise glandular epithelium may be restored after loss, provided the basement membrane on which it rests is not changed. After destruction of liver-tissue the epithelium of the bile-ducts (Fig. 138) proliferate, and the cell-division may extend to a relatively great distance from the site of injury. Experimental wounds of the liver heal through the formation of connective tissue, into which offshoots of the bile-ducts penetrate, while local reproduction of liver-tissue does not take place. Likewise, in the kidneys,

testicles, thyroid, and ovary the production of glandular tissue in the connective-tissue scar is slight or wanting, and does not lead to the formation of functionating tissue. In the salivary and mucous glands,
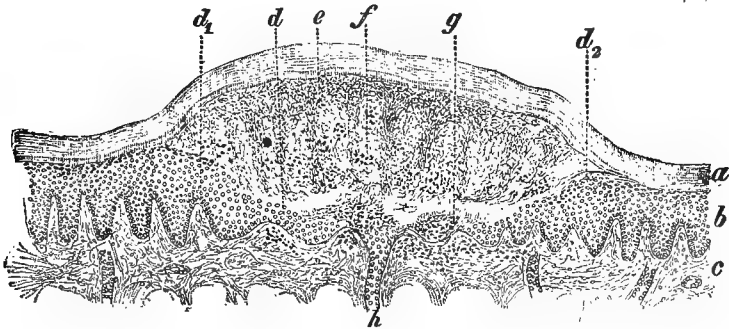
FIG. 139.—Healing of blister caused by a burn (alcohol, alum-carmine). Section through the skin of a cat's paw, forty-eight hours after the production of a blister. *a*, Horny layer; *b*, rete Malpighii; *c*, corium; *d*, newly formed epithelium; *d₁, d₂*, newly formed epithelium already differentiated into different layers; *e*, old, degenerated epithelium; *f*, pus-cells; *g*, exudate; *h*, sweat-glands. × 25.

on the other hand, branching of the gland-ducts is followed by the formation of new alveoli.

When portions of the mucosa and submucosa of the intestine are lost as a result of ulcerative processes, there occurs during healing glandular proliferation, which, according to the nature of the defect, forms partly typical, partly atypical (Fig. 118, *i*) glands that grow into the submucosa.

FIG. 140.—Development of blood-vessels by formation of offshoots; from preparations taken from inflammatory granulations. *a, b, c, d*, Different forms of offshoots, some solid (*b, c*), others becoming hollow (*a, b, d*), some simple (*a, d*), some branching (*b, c*), some without nuclei (*a, d*); some with nuclei (*b, c*); *d*, offshoot to which fibroblasts have applied themselves.

The new formation takes its start from the old glands, whose epithelium pushes over the edge and base of the ulcer (Fig. 118, *g, h*) and lines any depressions which may be present (*k*). In similar manner ulcerative defects of the gastric mucosa are made good; and even extensive ulcers may become covered with gland-containing mucosa, although the glands seldom attain mature development.

The epithelial portions of the uterine mucosa which are lost, as a physiological process, during menstruation and parturition, are restored in a manner similar to the healing of pathological defects of the endometrium. The new-formation of epithelium takes its origin from the glandular remains.

Compensatory hypertrophy of a kidney or liver is brought about through *the enlargement of existing renal tubules, or liver-columns respectively.* After wounds or other injuries of the liver and kidney it is highly doubtful if regeneration of functionating parenchyma ever occurs.

§ 82. If tissue is to be reproduced in considerable amount, the presence of blood-vessels is essential, since it is only through these that sufficient nutrition can be brought to the growing tissue.

The development of new blood-vessels takes place through the **formation of offshoots** from pre-existing vessels (Fig. 140). In the vessel-wall there occurs **proliferation of the endothelium** (Fig. 141), in which division of the nucleus occurs by **karyomitosis.**

FIG. 141.—Two vessels of the papillary body, whose endothelial cells are in process of proliferation (six days after painting the back of the foot with tincture of iodine) (Flemming's solution, safranin, and picric acid). *a,* Nucleus with chromatin framework; *b, b₁,* skein-forms; *c,* mother-star; *d,* connective-tissue cell with nuclear division-figure; *e,* lymphocytes. × 350.

As the first step in the formation of a new vessel, there is seen on the outer side of some capillary loop a tent-like elevation which terminates in a fine protoplasmic thread standing out from the vessel (Fig. 140, *a*), and gradually becoming longer and longer. There is thus formed at the beginning an arch of granular *protoplasm, which ends in a protoplasmic thread (a), and after a time comes to contain nuclei.* This thread may penetrate into another vessel, or unite with some other arch which it meets, or may finally return to the same vessel from which it started.

Further, from the solid arch itself new secondary arches may spring (Fig. 140, *b, c*), or at its end there may be formed a club-shaped swelling (*c*).

The originally solid arch becomes hollow after a certain time (*b, a*) through liquefaction of its central part, and the space thus formed immediately or soon comes to communicate with the lumen of the blood-vessel (*a*), or else there is developed an extension of the vessel-lumen into the arch. The blood of the mother-vessel finds its way at once into the daughter-vessel and widens it. As the hollowing-out process advances and extends to the point of entrance of the protoplasmic arch into another vessel, there is finally formed a new capillary loop permeable for blood.

Immediately after the opening of a way for the blood the capillary tube possesses a homogenous wall. After a certain length of time the protoplasm groups itself about the nuclei, which have in the mean time divided and multiplied in the wall, so that ultimately the capillary comes to be made up of flattened endothelial cells. As Arnold has shown, the boundaries of the individual endothelial cells may be made visible through the injection of a solution of silver into the vessel. At this time the wall for the greater part appears thickened, partly from proliferation of the cells of the vessel-wall, but also from the fact that formative cells from the neighborhood heap themselves on the surface of the young vessel (Fig. 140, *d*), adapt themselves to the wall, and so strengthen it.

At the time of the formation of the offshoots, the endothelial cells of the capillaries are swollen, and often reach such a size that the cross-section of a capillary looks not unlike a gland-tube lined with epithelium (Fig. 142, *d*). At the same time mitotic figures appear in the endothelium (Fig. 141, *a–c*), and later division of the nucleus and cell-protoplasm takes place.
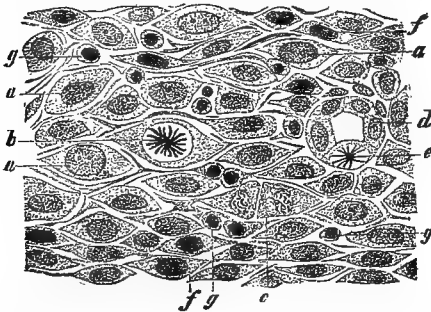
FIG. 142.—Proliferating periosteum, four days after fracture of a bone (Flemming's solution, hæmatoxylin). *a*, Osteoblasts with large nuclei; *b*, osteoblast with division-figure; *c*, two cells shortly after division, showing thread-skein in nucleus; *d*, blood-vessel with proliferating endothelium; *e*, endothelial cell with nuclear division-figure; *f*, large lymphocytes; *g*, small lymphocytes. × 350.

In what relation this proliferation stands to the formation of the offshoots is not clearly understood; but doubtless the latter spring from proliferating cells and represent cell-processes. The proliferation of endothelium, on the other hand, does not always lead to new vessels, but may result only in thickening of the vessel-wall and finally in obliteration of the lumen.

In the transformation of newly formed capillaries into arteries and veins the increase of tissue is, the result of continued proliferation of the cells of the vessel-wall. The *muscle-fibres* first appearing in the outer wall of the capillary tube are finely-branched cells whose nuclei lie parallel to the long axis of the capillary and whose processes surround the endothelial tube. After about fourteen days *elastic fibres* may appear in new-formed vessels (arteries).

It is difficult to decide whether the *new-formation of blood-vessels* is intracellular through the hollowing out of the solid buds of a single cell or whether it is intercellular through the formation of a space between two cells. The offshoots from the sides of the vessel-wall or from the end of the vessel give the impression of solid cell processes, but the possible participation of the protoplasm of two cells in the formation of such processes cannot be excluded.

The *new-formation of lymph-vessels* in new connective tissue is intercellular.

Literature.

(*New-formation of Blood-vessels.*)

Arnold: Die Entwicklung d. Blutcapillaren. Virch. Arch., 53 Bd., 1871; 54 Bd., 1872.
Flemming: Theilung von Pigmentzellen u. Capillarwandzellen. Arch. f. mikr. Anat., 35 Bd., 1890.
Mayer: Muskularisierung der Kapillaren. Anat. Anz., xxi., 1902.
Maximow: Entzündl. Neubild. v. Bindegewebe. B. v. Ziegler, Supp. v., 1902.

§ 83. The **connective-tissue structures** are almost all capable of both hyperplastic and regenerative proliferation. This is especially true of formed connective tissue, and periosteum and endosteum; while cartilage possesses but slight regenerative capacity, and fully developed
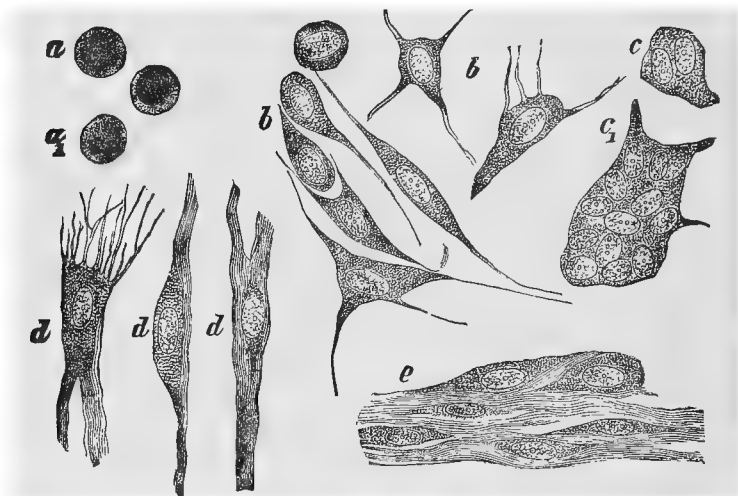
Fig. 143.—Isolated cells from a granulating wound (picrocarmine). *a,* Lymphocyte; a_1 polynuclear leucocytes; *b,* different forms of mononuclear fibroblasts; *c,* formative cell with two nuclei; c_1, multinuclear formative cells; *d,* fibroblasts in stage of connective-tissue formation; *e,* fully developed connective tissue. × 500.

bone none at all. Usually proliferating fibrous connective tissue gives rise to fibrous tissue, both in independent formations of connective tissue and in the supporting tissue of the glands, lungs, lymph-nodes, etc. The periosteum, bone-marrow, perichondrium and cartilage produce in addition to fibrous connective tissue and marrow-tissue also cartilage and bone.

Hyperplastic and regenerative proliferations of connective tissues are ushered in by *cell-division* in the course of which karyomitoses occur.

After injuries of the tissue these proliferations begin soon, for example, in wounds of the skin, or in fractures of bones; in the latter case even as early as the second day single cells of the periosteum become enlarged and show division-figures. Besides mitoses, direct division of nuclei takes place.

When only a few cells are destroyed newly formed cells replace them without the occurrence of marked structural changes in the tissues. If, on the other hand, a considerable amount of new tissue is produced in a short time, the proliferating cells form **embryonic tissue** consisting of cells, blood-vessels, and fibrillated ground-substance (Fig. 142). The extent of such formation naturally varies and is dependent partly on the capacity of the tissue for proliferation, and partly on the lesion leading to the proliferation.

FIG. 144.—Development of connective tissue from fibroblasts (Müller's fluid, picrocarmine). *a,* Fibroblasts; *b,* hyaline ground-substance with scattered fibrillæ; *c,* fibroblast with adjacent fibres. × 400.

Proliferating cells are always larger than the cells of fully developed, resting connective tissue. They contain one, sometimes two large, bladder-like nuclei with nucleoli, (Figs. 142, 143), though multinuclear cells (Fig. 143, c_1), so-called *giant-cells,* also occur. In association with proliferating cells there are often cells that have escaped from the blood vessels, but which take no part in the formation of the new tissue.

All those cells which are the antecedents of future tissue are designated **formative cells;** those giving rise to fibrous connective tissue are called **fibroblasts** (Figs. 143, *b, c, d, e;* 144, *a*), those forming cartilage and bone are known as **chondroblasts** (Fig. 146, *a, c*) and **osteoblasts** (Fig. 142, *a, b, c*) respectively.

The shape of formative cells varies greatly (Fig. 143, *b, c, d, e*), and is dependent, partly on spontaneous changes of form and partly on the

FIG. 145.—Scar of the skin, two years old, showing newly formed elastic fibres (alcohol, orcein). *a,* Corium with normal elastic fibres; *b,* scar with newly formed elastic fibres. × 500.

influence of environment, which under certain conditions compels the cells to take definite forms. The cells producing connective tissue usually present the greatest variety of form.

When **connective tissue** is developed from cellular embryonic tissue, *fine fibrillæ* (Fig. 143, *d, e*) appear in certain parts of the cell-protoplasm, or there is formed a *homogeneous intercellular substance* (Fig. 144, *b*) in which fibrillæ later appear. The formative cells at the same time diminish in size, and lie, for the most part, in small clefts (Fig. 143, *e*) in the ground-substance.

Elastic fibres appear in newly formed connective tissue at a late stage, about three weeks at the earliest, and at the beginning form fine
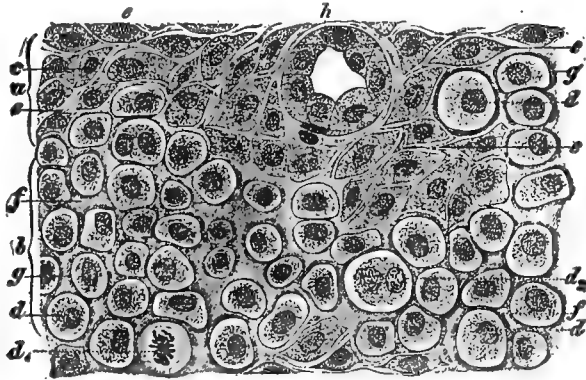
FIG. 146.—Periosteal formation of cartilage in a fracture five days old (Flemming's solution, hæmatoxylin, glycerin). *a*, Cellular embryonic tissue; *b*, cartilage; *c*, proliferating periosteal chondroblasts; *d*, cartilage-cells; *d₁*, *d₂*, nuclear division- figures in cartilage-cells; *e*, ground-substance of embryonic tissue; *f*, ground-substance of the cartilage; *g*, capsule of cartilage-cells; *h*, proliferating endothelium of a blood-vessel. × 320.

fibrillæ, which (Fig. 145, *b*) represent processes of older fibrils (*a*) and in part arise independently. They are a differentiation product of the ground-substance and have no relation to the cells.
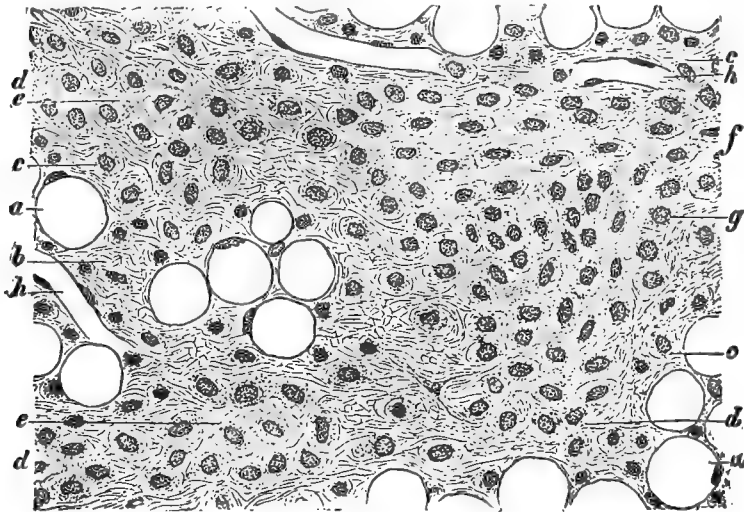
FIG. 147.—Endosteal formation of bone from masses of osteoblasts (Müller's fluid, picric acid, hæmatoxylin, carmine). Preparation from the inner callus of a fourteen-day old fracture of the fibula of a man twenty-five years of age. *a*, Fat-cells of the endosteum; *b*, endosteum containing no fat; *c*, scattered osteoblasts; *d*, groups of osteoblasts; *e*, first step in the formation of the ground-substance of bone; *f*, developing trabeculæ of bone; *g*, layer of osteoblasts lying upon the newly formed trabeculæ of bone; *h*, blood-vessel. × 150.

They develop most abundantly in newly formed connective tissue in the blood-vessels and in the skin, but also in other regions, for example, in connective-tissue proliferations of glands, serous membranes, etc.

In the development of **hyaline cartilage** there appears between the cells a hyaline basement-substance (Fig. 146, *f*), while the *chondroblasts* (*c*) assume a more rounded form (*d*). In time the ground-substance increases, the chondroblasts grow smaller and lie in rounded cavities whose walls are denser than the rest of the ground-substance and later form the part of the basement-substance called the *cartilage-capsule* (*g*).

In the development of **bone** from cellular embryonic tissue there appears between the formative cells a dense homogeneous or fibrillated
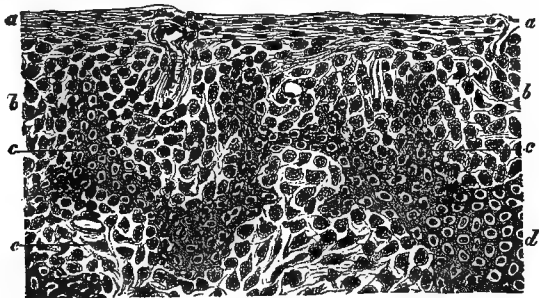
Fig. 148.—Formation of osteoid trabeculæ from the proliferating periosteum. Preparation from a fourteen-day old fracture (Müller's fluid, picric acid, hæmatoxylin, carmine). *a*, Fibres belonging to the outer periosteum; *b*, embryonic tissue; *c*, osteoid tissue; *d*, cartilage; *e*, bone-marrow. × 75.

basement-substance (Figs. 147, *e*, *f*; 148, *c*), **osteoid tissue,** which becomes impregnated with lime-salts and transformed into **bone.** When the ground-substance between the osteoblasts is of a loose fibrillar nature (Fig. 147, *d*) the transition into osteoid tissue is brought about through thickening of the ground-substance (*e*, *f*). The *osteoblasts* lie in spaces of irregular outline (Figs. 148, *c*; 149, *b*), and are known as *bone-corpuscles.* In extensive development of cellular embryonic tissue the change into bone is limited to certain parts of the tissue, and trabeculæ

Fig. 149. — Formation of bone, through deposits made by osteoblasts upon the surface of old bone (Müller's fluid, picric acid, hæmatoxylin, carmine). *a*, Old bone; *b*, newly formed bone; *c*, osteoblasts. × 260.

(Fig. 148, *c*) are formed, which do not undergo full development into bone and are not calcified, so-called **osteoid trabeculæ.** The embryonic tissue (*b*) lying between becomes changed into **marrow-tissue,** the cells being united to each other through processes, while between them there appears a fluid basement-substance, in which round-cells later are embedded. If bone-tissue is to be deposited around old bony trabeculæ, the *osteoblasts* (Fig. 149, *c*) arrange themselves on the surface of the latter, and later produce bone (*b*) which appears as a lamella.

Fibrillated connective tissue, bone, and cartilage are closely related and one may be transformed into the other (see § 88).

Mucous tissue arises from embryonic tissue through the formation of a mucin-containing, homogeneous, gelatinous basement-substance between the cells, which become united through processes to form a network.

15

Lymphadenoid tissue can develop from embryonic tissue through the formation of a supporting reticulum in which lymphocytes gather. In *injured lymph-nodes,* the cells of the reticulum proliferate and form *fibrous tissue;* development of this connective tissue into lymphadenoid tissue either does not take place at all or but to a very slight degree.

Spleen-tissue is not formed anew after injury; the wound heals through *cicatrization,* nor does compensatory hypertrophy take place after the removal of large portions of the organ.

Fat-tissue arises through the taking up of fat into fibroblasts, the cells becoming changed through the confluence of the infiltrated fat-droplets.

The **basement-substance** of the tissues described above is a **product of the protoplasm of the formative cells.** Whether portions of the cell-protoplasm are changed directly into intercellular substance, or whether they secrete the latter, or separate it from the intercellular fluid, is a difficult question to answer; it is probable that only the first two methods of formation occur.

Fibrillar connective tissue can develop from any connective tissue possessing the power of proliferation, but there must first be formed an intermediate stage of embryonic tissue.

Bone arises from the periosteum, perichondrium, and endosteum, but may also develop from other connective-tissue substances, for example, from the inter-muscular connective tissue and the connective tissue of blood-vessels.

Cartilage arises from proliferating perichondrium, periosteum, endosteum, and from cartilage itself; but may also be developed from other connective tissues, for example, the connective tissue of the testicle and parotid.

New *lymphadenoid tissue* may, under pathological conditions, arise either from lymphadenoid tissue or fat-tissue (*Bayer*) or from fibrillated connective tissue. It is formed from the latter most frequently in the connective tissue of the mucosa and submucosa of the intestinal tract, as well as in the glandular organs; rarely in the intermuscular connective tissue. New hæmolymph-nodes are formed in adipose tissue after splenectomy (*Warthin*).

Mucous tissue may develop from any proliferating connective-tissue substance, but rarely appears in large masses, and is usually a transitory form passing over either into fat or connective tissue.

Fat-tissue develops particularly in those regions normally containing fat, but occurs also at times in other places, for example, in the reticular connective tissue of atrophic lymph-nodes, in the perimysium internum of atrophic muscles, etc.

The close relationship of the connective-tissue substances to each other enables the different forms to pass from one to another without the need of an intermediate stage of embryonic tissue produced by proliferation. Further details in regard to this point are contained in § 88.

§ 84. The **regeneration of red blood-cells or erythrocytes** occurs through mitotic division of nucleated young forms known as **erythroblasts** (Bizzozero, Neumann, Flemming). In the adult this new-formation is restricted to the bone-marrow, and this is true also of other mammals, birds, reptiles, and tailless amphibians, while in the tailed amphibians and in fishes the spleen also shares in the process. In embryonic life the formation of the red blood-cell takes place throughout the vascular system, but later becomes restricted to the spleen, liver, and bone-marrow, and finally to the bone-marrow alone.

The entrance of the red blood-cell into the circulation takes place after loss of its nucleus.

In increased new-formation of red cells following loss of blood, as well as in chronic anæmias, nucleated red cells may appear in the circulating blood. The fatty marrow may again take on the character of

splenoid marrow, this change being accomplished by congestion of the blood-vessels with increase in the red cells of the marrow, while the fat in the recticulum disappears.

The **new-formation of colorless cells of blood and lymph,** the **leucocytes,** occurs in the lymph-nodes and in the lymphoid deposits in the mucous membranes and spleen; and in the bone-marrow. The mononuclear cells, known as *lymphocytes,* develop almost exclusively in lymphoid foci, in the germinal centres of which mitoses may not in-

frequently be found. (Fig. 150). The *poly-nuclear leucocytes* and *eosinophile cells,* on the other hand, are formed in the bone-marrow. Whether the large cells with clear nuclei known as *mononuclear leucocytes,* and the *transition-forms* with horseshoe-shaped nuclei, are formed in the bone-marrow is doubtful. They are often regarded as lymphocytes.

A **pathological increase of the colorless cells (leucocytosis)** may take place through increased emigration of cells from the forma-tive tissues without actual increase in cell-production. Long-continued persistence of such an efflux, however, presupposes in-creased production.
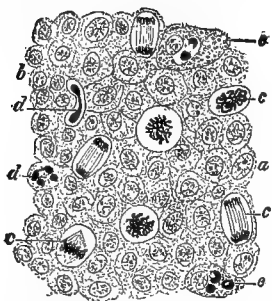
Fig. 150. — Section from the germinal centre of mesenteric gland (after Flemming). *a,* Large; *b,* small lymphocytes; *c,* karyomi-toses; *d,* direct nuclear division or nuclear fragmentation; *e,* cells containing near the nucleus "tin-gible bodies" and small yellow pigment granules, whose signifi-cance is unknown. × 400.

Transitory increase in the white cells is designated *leucocytosis,* while a permanent one is called *leukæmia.* The former is characterized by increase in the neutrophile polynuclear leucocytes, rarely by increase in the lymphocytes. Two forms of leukæmia are distinguished: *lymphatic leukæmia,* in which the lymphocytes are increased, and *myeloid leukæmia,* characterized by the appearance in the blood of *myelocytes,* mononuclear cells arising in the bone-marrow and provided with neutrophilic or eosinophilic granules.

§ 85. The **regeneration of transversely striated muscle** takes its start from portions of old muscle-fibres; and although, after injury to a muscle, the intermuscular connective tissue may be excited to prolifera-tion, there is formed only connective tissue, or probably the sarcolemma of new fibres, but never new contractile substance.

The first signs of formative activity in muscle-fibres after injury ap-pear in the nuclei, which become elongated and divide into a varying number of fragments. Mitotic division occurs early and seems to be the only way in which multiplication takes place.

The behavior of the contractile substance of the muscle differs ac-cording to the nature and extent of the injury. In traumatic, toxic, and anæmic injuries it suffers fragmentation, so that the muscle-cells lie between the detritus of the muscle-fibres. Crushing and tearing bring about separation of the contractile substance. The ends of the muscle-fibres, in such case, may be conical, oblique, transverse, or irregular, but not infrequently become split into pointed filaments (Fig. 151, *a*).

Mitotic division takes place, not only in nuclei that rest on living fibres (*a*), but also in the muscle-cells between the separated fibres (*b*); and in both places leads to the production of large cells, which form multinuclear masses at the ends of the muscle-fibres (*e, f*) as well as in

the body of the fibres (*c*). Into these the transversely striated muscle-substance passes without a sharp line of demarcation. There occurs, there-fore, *with the multiplication of nuclei an increase of the sarcoplasm of the muscle-fibres.*

The muscle-cells not connected with living contractile substance be-come changed into *cells with large nuclei* (*b*). Through continued divi-sion of the nucleus these cells become transformed into *multinuclear protoplasmic masses* (*d*); a scar in muscle tissue from eight to thirty
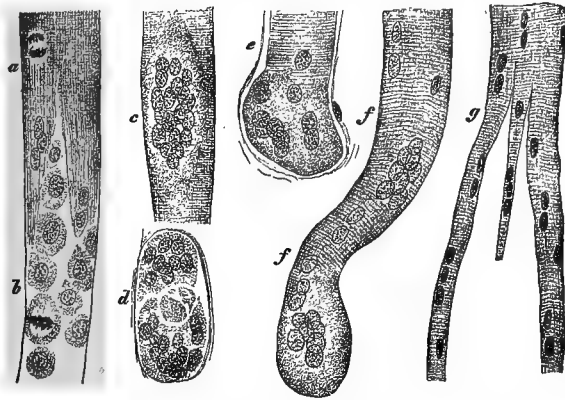
FIG. 151.—Portions of muscle-fibres showing regenerative proliferation, from muscle-wounds of different ages (Flemming's, safranin). *a*, Pointed ends of the split stump of a muscle-fibre, with nuclear division-figures, three days after laceration of the muscle; *b*, proliferated muscle-nuclei transformed into cells rich in protoplasm, one of which is in process of mitotic division; *c*, piece of a muscle-fibre eight days after tying the muscle; *d*, giant-cells, enclosing necrotic pieces of muscle, from a muscle scar twenty-six days old; *e*, *f*, muscle-fibres ending in proto-plasmic masses (muscle-buds), *e*, from a muscle scar ten days old; *f*, from one twenty-one days old; *g*, dividing muscle-fibres from a muscle-scar forty-three days old. × 315.

days old, contains giant-cells which often enclose the remains of old mus-cle-fibres (*d*) in large numbers.

New muscle develops for the greater part from the richly nucleated sarcoplasm, which appears in and at the ends of the fibres, and through increase of size causes increase in the thickness and length of the mus-cles. With the transformation of the sarcoplasm into fibrillæ there gradually appears longitudinal and later transverse striation, a sign that the structure has completed its development in the way characteristic of muscle.

The greater number of *proliferating muscle-cells which have no con-nection* with living fibres die; but it is to be noted that they persist for a long time, so that not infrequently there may be seen in muscle-scars from eight to forty days old protoplasmic masses rich in nuclei. These may form long, connected bands, or rows of separate pieces of proto-plasm. There can be no doubt that certain of these cells become trans-formed into transversely striated muscle-substance; this takes place by the formation of new and independent muscle-fibres or by union with old muscle-fibres or muscle-buds. The formation of disconnected muscle occurs particularly when the contractile substance is destroyed while the sarcolemma remains intact (as in Zenker's degeneration in typhoid fever). On the other hand, the formation of buds is observed especially at the ends of fibres which have been divided.

The buds springing from the ends or sides of muscle-fibres may cause simple elongation of the fibre, frequently deviating from its original direction (*f*). Often there are fibres which have split into two or three parts (*g*), and thus pass into the muscle-scar. As far as we know, this splitting of the fibre occurs early (*a*), before the proliferating muscle-nuclei have formed much sarcoplasm, so that proliferation appears first in the split portions. As a result of such splitting a muscle-scar may contain a greater number of muscle-fibres than were originally present in the affected area.

Hypertrophy of *transversely striated muscle* takes place through enlargement of the individual fibres; the thin muscle-fibres in particular becoming increased in thickness. The nuclei do not increase in number. On the other hand, nuclear increase does take place in growth in the length of the muscle; and is the result, most probably, of amitotic division (Morpurgo).

Regeneration of heart-muscle has not been positively demonstrated. After injuries of the heart, division figures appear in the muscle-cells, but after a few days these can no longer be demonstrated, and the wound heals through the formation of ordinary scar-tissue. Focal degenerations of the myocardium likewise heal by connective-tissue cicatrization.

New-formation of smooth muscle-fibres occurs after traumatic or toxic and ischæmic degeneration. It occurs also in muscle tumors and is initiated by mitotic division of the nuclei, followed by division of the cells. According to the results of experimental work and of observations on the muscle tissues of man, the reproduction of fibres after injuries and focal degenerations is slight, ceasing after a short period. Thus, defects in the muscularis of the stomach and intestines or of the bladder are, for the most part, closed by connective tissue.

Hypertrophy of smooth muscle-fibre is a phenomenon of frequent occurrence. In the pregnant uterus the muscle-cells may reach five to ten times the ordinary size. Of other organs the bladder most frequently shows marked hypertrophy of smooth muscle.

§ 86. **Regeneration of the nerve-elements of the central nervous system through the reproduction of ganglion-cells** most probably does not occur in man and mammals in post-embryonal life. According to the investigations of Stroebe, on the other hand, *divided nerve-fibrils* (in mammals) *may grow lengthwise to a certain extent through sprouting of the axis-cylinder;* this is particularly true of the fibres of the pyramidal tracts and the posterior roots, both of which after being divided grow into the scar-tissue at the site of the wound, the former in a downward direction, the latter upward. Complete restoration of nervous tissue does not take place, and a defect in the spinal cord due to trauma is replaced partly by connective-tissue, in part by neuroglia. According to Borst, new axis-cylinders may be formed within the new neuroglia in the neighborhood of cerebral lesions, and medullary nerve-fibrils may be produced by the outgrowth of old fibres.

Regenerative and **hypertrophic proliferations of neuroglia** are phenomena which occur frequently in diseased conditions of the central nervous system, and follow degenerative changes of the nervous elements, or destruction of the neuroglia, or they may appear without such antecedents, in the latter case arising during the period of development.

The new-formation is brought about by mitotic division of the nuclei and bodies of the glia- or of the ependyma-cells.

The newly formed glia-cells produce a profusion of delicate fibrillar processes (Fig. 152, *a*), and, as in the normal tissues of the central nervous system, t h e r e may be distinguished a m o n g these two v a r i e t i e s of cells which are known as *astrocytes* (Deiter's cells), the so-called "*m o s s y   c e l l s*" (*Kurzstrahler*) and "*spider-cells*" (*Langstrahler*) with long, stiff, l e s s - f r e e l y branching processes (*a*). The processes

FIG. 152.—Sclerotic tissue from the posterior columns of a case of multiple sclerosis (Müller's fluid, Mallory's method). *a,* Glia-cells with numerous processes, seen in longitudinal section; *b,* sclerotic tissue with transversely cut glia fibres. × 500.

of these cells form sometimes a loose, sometimes a dense felt-work of fine fibrillæ (*a, b*) in which the cells, which have but little protoplasm, are embedded. After full development of the tissue separation of the processes from the cell-bodies may take place. The thickening of the tissue caused by the proliferation belongs to the process known as *sclerosis*.

FIG. 153. — Old and newly formed nerve-fibres from an amputation-stump, in longitudinal section (Müller's fluid, Weigert's stain). *a*, *b*, Old nerve-fibres, from which several young nerve-fibres have grown; *c*, neurilemma with young nerve-fibres. × 180.

Regenerative new-formation of the nerve-fibres of the peripheral nervous system is of frequent occurrence and takes place in all those cases in which the continuity of a nerve-fibre is entirely or partially interrupted. For its accomplishment, however, it is necessary that the ganglion-cells whose processes form the nerve-fibres in question be preserved.

When a nerve has been severed, the axiscylinders and medullary sheaths, in the distal portion, undergo degeneration, the latter breaking up into drop-like detritus, which later is dissolved. During the disintegration of nerve-fibres the nuclei beneath the sheath of Schwann undergo mitotic division and form cells rich in protoplasm, which may take up the products of destruction of the nerve-fibres.

Of the proximal portion of the nerve the peripheral extremity alone degenerates, as far as the next Ranvier's node, or the one beyond.

The **regeneration of nerves** begins a few days after the operation, in the proximal portion, about 0.4–2 cm. above the cut end.

The first change consists in swelling of individual axis-cylinders in the peripheral parts of the nerve-bundle of the proximal end, which is followed by splitting-off of two to five or more new axis-cylinders. The axis-cylinders arising in this way from the old ones grow in a longitudinal direction (Fig. 153, *a, b*) and form, within the sheath of Schwann, whole bundles (Figs. 153, *c;* 154, *e*) of newly formed nerve-fibres, which fill the old nerve-tubes, and indeed stretch them; sometimes remains of old fibres are visible in the same sheath (Fig. 154, *f*). Single fibres may even break through the old sheath of Schwann, and then extend further in the endoneurium, or penetrate the perineurium into the epineurium.

FIG. 154.—Cross-section of a nerve-bundle of the median nerve just above a wound dividing the nerve, made four months previously (Müller's fluid, carmine). *a,* Perineurium; *b,* endoneurium; *c,* cross-section of a vessel; *d,* old unchanged nerve-fibre; *e,* bundle of newly formed nerve-fibres; *f,* newly formed nerves, with remains of old fibres inside the same sheath. × 200.

In this way there are formed on the lower end of the proximal portion of the nerve a large number of new nerve-fibres, which in the beginning consist only of the newly formed axis-cylinders, but immediately surround themselves with a medullary sheath, which by reason of its irregular development gives to the nerve-fibres a varicose appearance (Fig. 153, *c*). Later the fibres acquire a neurilemma-sheath — that is, a connective-tissue covering which is probably formed from the nerve-corpuscles concerned in the proliferation.

When a nerve is entirely severed and there is no possibility of union with the distal portion — as, for example, occurs in all amputations — there is formed in the region of the cut end an embryonic tissue, springing from the connective tissue of the nerves, which later becomes changed into connective tissue. In the beginning free from nerves, this connective tissue becomes penetrated by young nerves growing out from the fibres of the nerve-stump,

FIG. 155.—Amputation-neuroma of the sciatic nerve, in longitudinal section (amputation of nerve nine years previously) (Müller's fluid). *a,* Nerve; *b,* neuroma. × 3.

which, arranged in small bundles, or scattered, grow into the connective tissue in every direction (Fig. 155). Not infrequently the growth of nerves is so extensive that nodular or clubbed swellings (Fig. 155, *b*) arise on the ends of the nerves. Such a swelling is known as an *amputation-neuroma*.

When a nerve after division is again united, or if the division is only partial, the nerve-fibres growing out from the proximal end, after penetrating the connective tissue formed in the wound, may in part, or all, find their way into the peripheral portion of the nerve where, in the mean time, the nerve-fibres have been destroyed. In this way the *distal end may again become neurotized* — that is, supplied by new nerves. According to investigations of Forssmann, the direction of the newly growing fibres is governed by chemotactic influences arising from the disintegration-products of the old nerve-fibres.

According to the investigations of Vanlair the growth of a regenerating nerve is about 0.2–1 mm. daily, according to the character of the tissue. A portion of the new nerve-fibres may penetrate into the old, empty sheath of Schwann; others extend into the epineurium and perineurium, and in this situation grow toward the periphery to the end-organ. Single fibres may pass by the end of the nerves, and grow toward the periphery, either along the old nerves or by an independent route. Many fibres, which leave the old route, are finally lost in the tissues. In the lower portion of the intermediate substance (Vanlair) the nerve-strands begin to collect into bundles again, and with the formation of a perineurium about the latter, the regenerated nerve takes on more and more the structure of a normal nerve.

The above-described process of regeneration requires for its accomplishment weeks or even months, and sometimes is not complete after several months.

The question of the **regeneration of the central nervous system** is still under discussion. It is generally accepted that in the cold-blooded animals, reptiles, and tailed amphibia, regenerative new-formation of portions of the central nervous system can take place. In warm-blooded animals, particularly in the mammals, the majority of experimental investigations have failed to demonstrate regenerative new-formation of ganglion-cells. *Tedeschi, Vitzou* and others, claim to have observed, after injuries of various kinds, both new-formation of neuroglia and of ganglion-cells and nerve-fibres; but the investigations carried out in my laboratory by *Tschistowitsch* seem to me to contradict these assertions. The results obtained by *Grunert* in experimental work with pigeons agree with the conclusions arrived at by *Tschistowitsch*.

Monti and *Fieschi* could demonstrate no evidences of regeneration in the ganglion-cells of the sympathetic after injuries. *Torelli* found only degenerative changes in the ganglion-cells of the intervertebral ganglion after injury.

The **new-formation of peripheral nerve-fibres** has been made the subject of experimental research, and different observers have come to different conclusions (see *Stroebe, l. c.*). The above-described mode of new-formation I regard as firmly established, in so far as its essentials are concerned, on the ground of personal investigations. I have been unable to confirm the views of *Neumann, Dobbert, Daszkiewicz, Cattani, Wier Mitchell, Gluck, Beneke, von Büngner, Wieting,* and others, who hold that the new fibres in the distal portion of the severed nerve rise autochthonously from the nuclei of the sheath of Schwann, or from the old axis-cylinder, or from a protoplasmic mass formed by chemical transformation of the medullary sheath and axis-cylinders (*Neumann-Dobbert*). The view held by *Bethe,* that the nerve-fibres arise without participation of the ganglion-cells in the fused ectodermic cells whose remains later represent the cells of Schwann, appears to me to have been shown by *von Kölliker* to be incorrect. Likewise, the attempt made by *Neumann* and *Wieting* (*Marchand*) to bring into accord the established

fact of the outgrowth of the axis-cylinders of the proximal portion into the scar uniting the severed ends, with the theory of the origin of new nerve-fibres from the nuclei of the sheath of Schwann, or from the remains of old fibres, or from both, by the assumption that the axis-cylinders growing from the proximal end convey a stimulus from the nerve-centres to the distal portion and thereby make possible the development of new fibres, I regard as unsuccessful, and hold to the above-given view. I am further of the opinion that the medullary sheath is not formed by the cells of the sheath of Schwann, but represents a product of the axis-cylinders. According to *Nissl, Marinesco,* and others (see *Barbacci, l. c.*) there occurs, after severing of a nerve, degeneration in the corresponding ganglion-cells with disintegration of the Nissl's bodies, and this may lead to the destruction of individual cells. Later, progressive changes with new-formation of chromatin take place, and may lead to hypertrophy of the cells (*Marinesco*) ; these changes reach their maximum in about ninety days, after which time there is a return to the normal condition.

The **regenerative new-formation of the tissues of the eye** has repeatedly been an object of research. According to *Wolff, Müller,* and *Kochs* the *lens* of tritons may regenerate, after removal, by proliferation of the epithelium of the inner layer of the iris. According to *Röthig,* the same thing occurs in the trout. *Gonin* observed in rabbits, after the lens had been removed in such a manner that the capsule and some of the equatorial lenticular fibres and epithelium of the anterior wall were left behind, that there occurred proliferation of this epithelium, leading to the union of the anterior and posterior walls through cells resembling connective-tissue cells. A new-formation of lenticular fibres from these cells does not take place. Remains of the lenticular fibres may form a rudimentary, useless lens, which in young animals may become somewhat enlarged through the growth of the fibres. *Randolph* obtained somewhat better results in guinea-pigs. In the human eye similar formations are seen after removal of the lens, and are known under the name of "Krystallwulst" (*Baas*). According to *Franke, Krückmann,* and *Stoewer,* the sclera possesses but slight power of proliferation. Wounds of the same are healed chiefly through proliferation of the choroid and episcleral tissue.

According to *Baquis,* there occurs, in the injured *retina* of the rabbit, division of both ganglion and neuroepithelial cells. According to *Krückmann,* the pigment-epithelium is capable of extensive regeneration, but neuroepithelium, on the other hand, is not again formed.

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III. The Results of Transplantation and Implantation of Tissues and Organs.

§ 87. The local regeneration of tissue is, as mentioned in the last part, often but slight, so that losses of tissue may be followed by permanent defects, and in place of the original structures there may appear only cicatrical tissue of lesser value. Consequently, many attempts have been made, through **transplantation** and **implantation** of tissue, to improve the healing-process; such attempts have in part been successful. At the same time they have thrown light on the individual life of the tissues and on the behavior of the organism toward implanted living tissue.

The most successful results have been obtained in the *transplantation of tissues which remain connected with their nutrient vessels,* since, at the point of union the transplanted portion and the fixed tissues grow together in essentially the same manner as do the edges of an incised wound. This method is utilized most frequently in plastic operations on the surface of the body, but it also finds application in internal surgery.

Transplantations of tissues completely freed from their basement-structures have been successfully performed. The cells of the epidermis are able to live for the longest time. Ciliated epithelium may be preserved for days and still show movements of the cilia. Next to the surface-epithelium stand the connective tissues, other tissues quickly die, the cells of the brain and kidney within a few hours after

obstruction to the blood supply. According to the investigations which have been made up to the present time the tissues of the skin, periosteum, inter-articular cartilages, muscle and cartilage most easily preserve their vitality. Morpurgo found cells of the periosteum to be capable of reproduction after seven to eight days. The vessels, tendons, and neurilemma appear to be even more resistant.

Transplantations of skin give the best results, and were first recommended by Reverdin and Thiersch for the healing over of open wounds
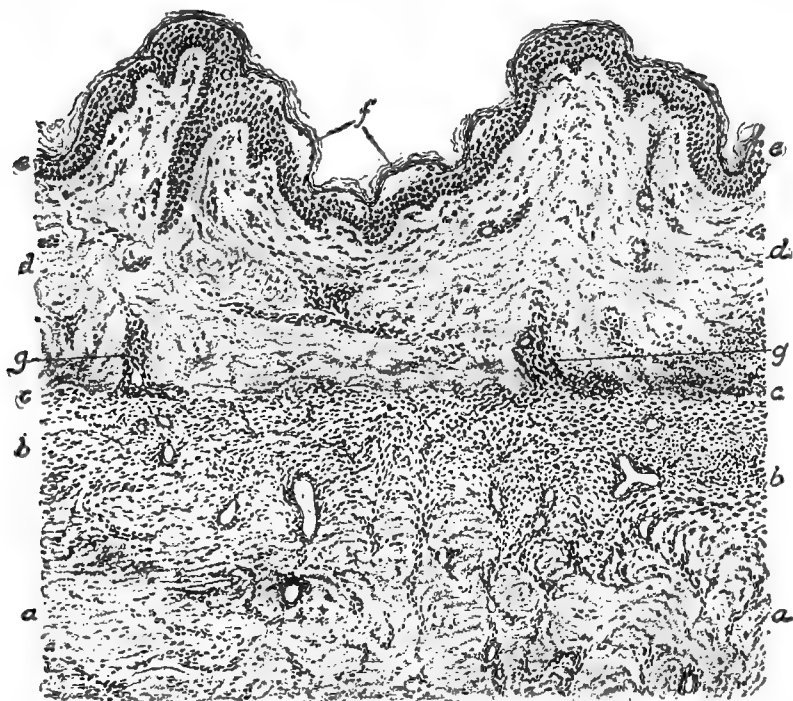
Fig. 156.—Skin-graft four and one-half days old (formalin, hæmatoxylin, picrofuchsin). *a*, Deep layer of the corium; *b*, proliferating granulation-tissue; *c*, boundary of proliferating zone; *d, e*, transplanted portion of skin; *f*, desquamation of the horny layer; *g*, vascular offshoots and granulation-tissue extending into the transplanted connective tissue. × 107.

and have since been extensively used for this purpose. The material used consists of pieces of skin taken from the same individual or from another person. Ordinarily, strips of skin removed by means of a sharp knife are used, and include the tips of the papillæ and the upper layers of the corium. Epithelium in connection with a thicker layer of the corium may also be successfully transplanted, and in injuries large portions of skin which have been completely torn off may be again joined to the deeper tissues on the same spot from which they were removed.

The transplantation may be made either on a fresh wound or on one showing proliferation. The strips of skin are held in place by mechanical means. The pieces of skin become fastened to the surface of the wound by coagulated blood or lymph. In successful cases union with the underlying tissue takes place in about eight days.

The nourishment of the transplanted pieces (Fig. 156, *d*) is obtained

from the fluids which exude from the underlying tissues. Later, there begins in the latter vascular connective-tissue proliferation (*b, c*), and the transplanted portion becomes penetrated from below by new blood-vessels (*g*) and by fibroblasts, so that it finally becomes interspersed with granulation tissue. Under favorable conditions the old vessels may again become opened through the ingrowth of new vessels.

The behavior of the transplanted portion varies in individual cases. *A part of the transplanted tissue is always lost (f). Other cells, both epithelial and connective-tissue, proliferate and produce new tissue.*

The outcome of a successful transplantation is the covering over of the area with epithelium and corium. Through the latter it is possible for the cicatricial area to possess papillæ. To what extent the superficial layers of the cutis arise from the graft or to what extent from the tissue upon which it is planted, cannot be determined. If the papillary bodies are preserved, a portion of the tissue may be formed from immigrating fibroblasts. After a time the transplanted area comes to contain nerves. The tactile sense is first restored (Stransky), later the sensibility to pain and temperature. New elastic tissue also develops, as in ordinary scars, from the ends of old fibres.

Besides skin-transplantations, there have been attempted transplantations of almost all the tissues: periosteum, bone-marrow, bone, muscle, nerves, thyroid, pancreas, adrenals, mammary gland, mucous glands, ovary, testis, etc.; also of tissue-combinations, for example, a rat's tail from which the skin has been stripped. Embryonal tissue has also been transplanted in a variety of ways. Finally the attempt has been made to transplant tissues from one animal to another of different species.

Such transplantations have been made on open wounds, in the subcutaneous tissues, peritoneal cavity, glandular organs and lungs, either by direct operative procedures or by the introduction of the tissue into the blood-stream.

The results of these experiments may be summed up as follows:

In all transplanted tissues there first occurs degeneration, and a part of the tissue dies. After a time there usually results *proliferation* of the remaining portion, which may lead to new-formation of tissue. Connective-tissue cells form new connective tissue; periosteum and end-osteum form bone or connective tissue; muscle-cells, new muscle; cartilage, new cartilage; surface epithelium, new epithelium (epithelial cysts). Of the glands the thyroid, mucous glands, and mammary glands may form new glandular tissue; such new-formation does not take place in the case of the kidney, liver, testis, and ovary. Of the liver only the epithelium of the bile-ducts proliferates. Only in the transplantation of the ovary into the peritoneal cavity of the same animal can the ova ripen and pregnancy occur (Knauer, Ribbert, Gregorieff). The tissues of young individuals in general show a greater capacity for proliferation than those of old ones. In the transplantation of complicated tissues, for example, the skinned tail of a rat, all the tissues may produce new tissue and the whole may grow.

Embryonal tissue can likewise grow after transplantation and become differentiated; cartilage, which in later life shows but little power of proliferation, is longer preserved and shows further growth, while the delicate soft tissue-formations easily die.

After a time there occurs in almost all transplanted tissues, as well as in the rewly formed tissue, *a retrograde change,* and they are *finally*

destroyed through the ingrowth of tissue from the neighborhood. The time at which this occurs varies with different tissues, and is dependent partly on the character of the tissue, and partly on surrounding conditions. Implanted surface-epithelium can remain permanently, and give rise to *epithelial cysts.* Portions of thyroid, mammary gland, and pancreas are preserved for a long time. Cristiani found pieces of thyroid intact two years after implantation. The majority of tissues, however, disappear in a few months. In glands which are not capable of proliferation the gland-cells die first. If all of the implanted piece is not destroyed it may become encapsulated.

Tissue of different species, when transplanted, does not grow, but is *destroyed* or *encapsulated,* sometimes quickly, sometimes slowly.

According to published observations, *the implantation of tissue does not lead to the formation of permanent tissue* except in transplantation of skin. Nevertheless, such implantation may have a transitory or permanent value. The implantation of thyroid or pancreas may for a time check the harmful consequences of the loss of these glands. Through implantation of tissue into a defect temporary filling of the latter may be produced, and the neighboring tissues are thus permitted to proliferate for a longer time, and to form a greater amount of new tissue along the framework afforded by the implanted portion, and so to close the defect completely. Bone (not connected with nutrient vessels) when implanted into a part of the skeleton is absorbed (equally so whether living or dead bone is implanted), and is replaced by new bone arising from the neighboring periosteum and endosteum. In this way there may be better healing of the defect; implantations of bone or cartilage may also be made use of in other tissues, for the stimulation of more abundant production of tissue for the purpose of filling tissue-defects.

The transplantation of nerves has never resulted in the new-formation of nerve from the transplanted piece. The attraction which the products of disintegration of a nerve (Forssmann) exerts on the axis-cylinders growing into a wound may be utilized to direct the course of growing nerves into certain channels.

IV. Metaplasia.

§ 88. **Metaplasia** is that process by which a *tissue is changed into another closely related* without the intermediation of embryonic or granulation-tissue. Metaplasias play an important rôle in the development of individual connective-tissue formations, particularly in bone, cartilage, and marrow-tissue. Through proliferation of the periosteum or endosteum there is produced ordinary fibrillated connective tissue which later undergoes metaplasia into osteoid tissue, bone, or cartilage. In the *metaplasia of connective tissue into osteoid tissue* there occurs without further cell-proliferation condensation of the ground-substance (Fig. 157, *a, b*) which leads by gradual transformation to an osseous ground-substance (*c*) staining red with carmine or eosin or fuchsin. Deposit of lime-salts (Fig. 158, *c*) completes the process of metaplasia into true *bony trabeculæ.*

In the metaplasia of connective tissue into cartilage the ground-substance becomes thicker but more clear and stains less intensely (Fig. 159, *c*) than the connective tissue (*b*). The cells increase in size and lie in round spaces. Such changes may be observed in the periosteum and endosteum as the result of traumatic or infectious processes or in

the new-formation of fibrous tissue associated with tumor formations (Figs. 157 and 159). In wounds of the trachea which are first closed by scar-tissue, cartilage may be later developed by proliferation of intact perichondrium and metaplasia into cartilage (Fig. 160, b).

If normal or pathological *new-formed cartilage becomes penetrated by*
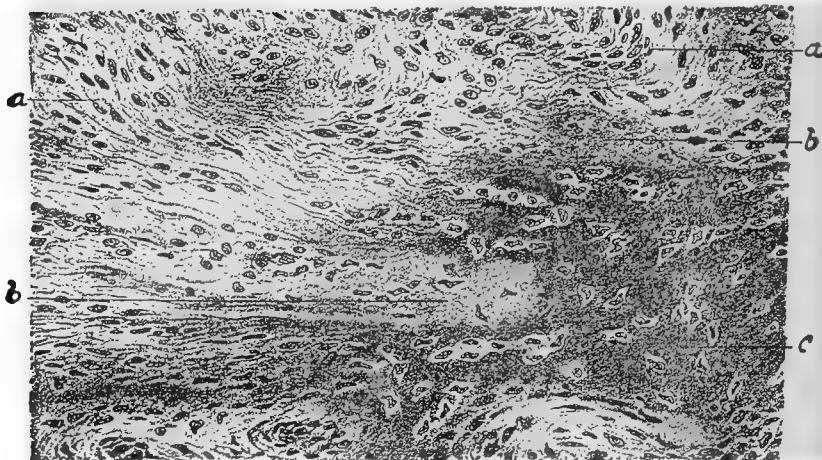
FIG. 157.—Periosteal formation of bone in a case of metastatic carcinoma of a rib. (Hæmatoxylin, picric acid, fuchsin.) a, Fibrillated connective tissue; b, connective tissue undergoing condensation; c, fully developed bone. × 300.

blood-vessels the ground-substance may undergo solution and the cartilage cells form reticular connective tissue with branched processes in the interstices of which certain cells gather, so that the whole takes on the character of bone-marrow; by taking up fat it may be transformed into adipose tissue (Figs. 161, b, c, and 162, f). If, in the vascularization of
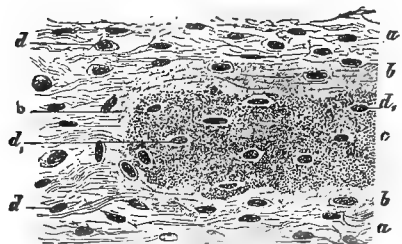
FIG. 158.—Formation of bone from connective tissue (alcohol, hæmatoxylin). Cross-section through a bone trabecula in process of formation; from an ossifying fibroma of the periosteum of the upper jaw. a, Connective tissue; b, thickened tissue, forming the groundwork of the new bone; c, deposits of lime-salts; d, connective-tissue cells; d₁, bone-cells. × 180.

cartilage, trabeculæ of cartilage remain, these may be transformed into *osteoid tissue* (Fig. 162, f) which when stained with hæmatoxylin and eosin takes an intense red stain, while the unchanged cartilage stains blue. Through the deposit of lime-salts it may later be changed into bone. In chronic inflammation of the joints, *cartilage may be transformed into ordinary fibrillated connective tissue*, particularly when its free surface is covered with connective tissue.

The metaplastic processes thus described are connected with preceding proliferations and may be associated with further appearances of proliferation. But there are metaplasias which have no connection with any proliferative change, or are only associated with it at a later period; thus myxomatous becomes changed into adipose tissue when the star-shaped tissue-cells become round through the taking up of fat, while the mucoid

ground-substance disappears. Lymphadenoid tissue may, after disappearance of the lymphoid elements, be changed into adipose tissue through the absorption of fat droplets by the cells of the stroma. Through
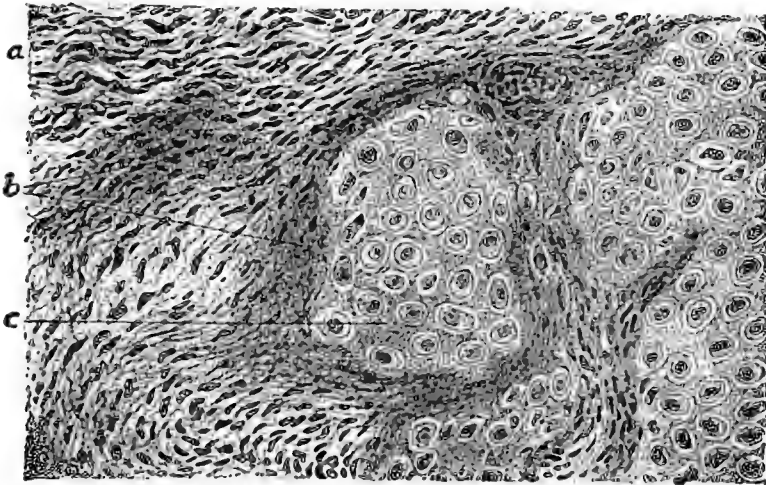
FIG. 159.—Periosteal formation of cartilage in metastatic carcinoma of a rib. (Hæmatoxylin, picric acid, fuchsin.) *a*, Fibrillated connective tissue; *b*, connective tissue undergoing condensation; *c*, fully developed cartilage. × 300.
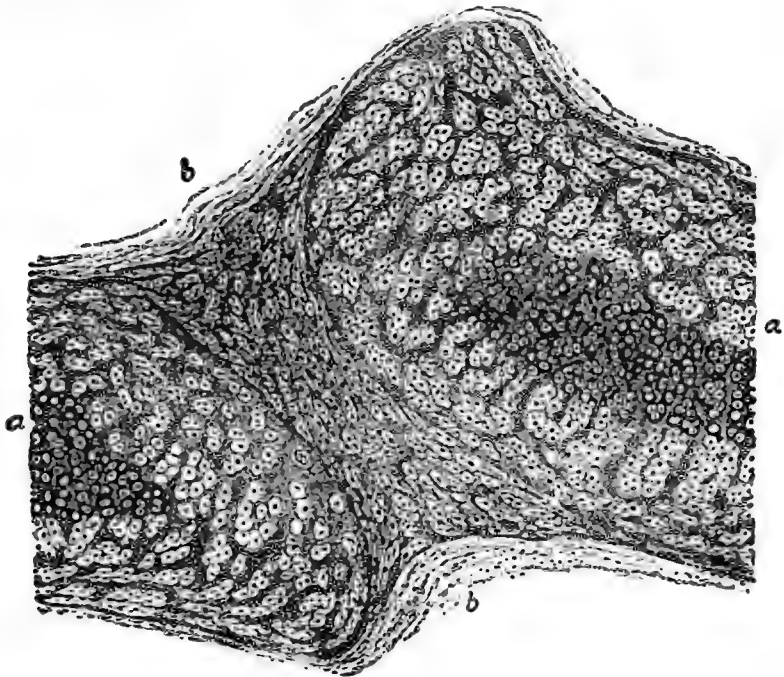
FIG. 160.—Healed tracheotomy wound in the cricoid cartilage, fifty-two days old. (Formalin, hæmatoxylin, and eosin.) *a*, Old cartilage; *b, b*, connective tissue arising from the perichondrium undergoing metaplasia into cartilage. × 60.

the disappearance of fat, adipose tissue may take on the appearance of mucoid tissue, and occasionally comes to contain mucin.

In the change of connective tissue into myxomatous tissue the fibrillæ
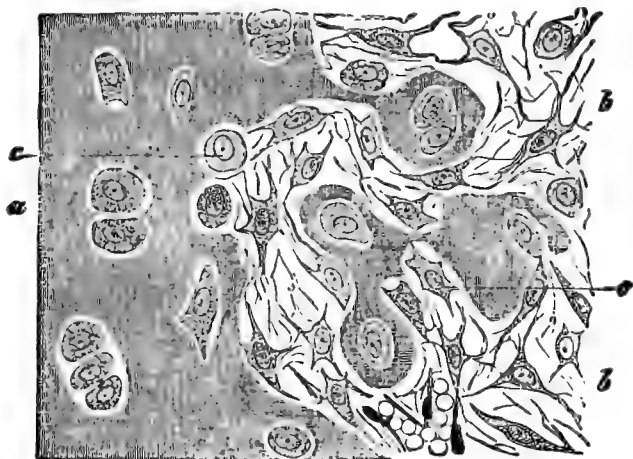
FIG. 161.—Metaplasia of cartilage into reticular tissue, in arthritis fungosa (alcohol, hæma-toxylin). a, Hyaline cartilage; b, tissue consisting of branched cells; c, cartilage-cells, set free by the liquefaction of the basement-substance of the cartilage, and becoming transformed into cells of mucous tissue. × 400.
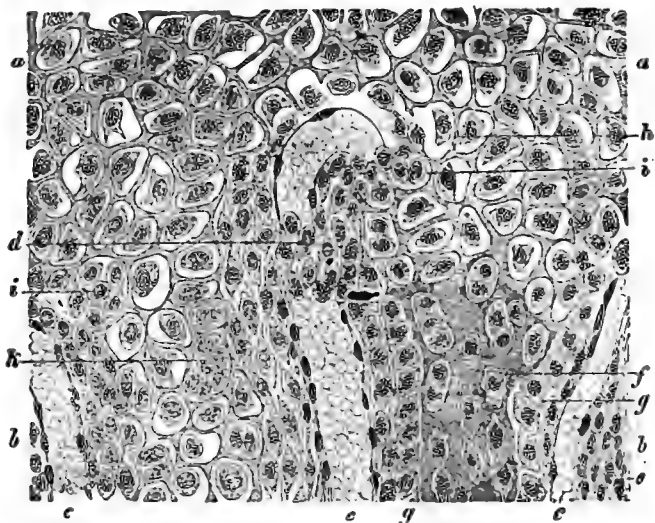
FIG. 162.—Metaplasia of cartilage into osteoid tissue, in a callus fourteen days old (Müller's fluid, picric acid, hæmatoxylin, carmine). a, Hyaline cartilage; b, marrow-spaces; c, blood-vessel; d, cellular, e, fibrocellular marrow; f, osteoid tissue; g, osteoblasts; h, cartilage-cells freed through the disappearance of the ground-substance; i, proliferating cartilage-cells in opened capsule; k, proliferating cartilage-cells in closed capsule. × 200.

vanish and there appears in their place a jelly-like mucus. If sufficient numbers of lymphoid cells collect in connective tissue and there occurs at the same time disappearance of the connective-tissue fibres, while

the connective-tissue cells unite through their processes to form a reticulum, lymphadenoid tissue is developed.

Epithelial metaplasia occurs most frequently in chronically inflamed mucous membranes, for example, uterus, urethra (gonorrhœa), nose (ozæna), and trachea, cylindrical being transformed into pavement epithelium.

This change occurs in the following manner: after repeated loss of epithelium the regenerating epithelium changes its character. In mucous membranes possessing stratified pavement-epithelium the upper layers may show cornification, not only in places which normally possess pavement-epithelium, as the tongue and cheeks, but also in those possessing transitional epithelium (the urinary tract), or cylindrical epithelium (nose, ureters, and gall-bladder). In connection with this phenomenon should be mentioned the fact that epithelial tumors arising in mucous membranes possessing transitional or cylindrical epithelium may bear the character of squamous-cell tumors.

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CHAPTER VII.

Inflammation.

I. The Early Stages of Acute Inflammation.

§ 89. Under the designation **inflammation** are grouped phenomena which represent a **combination of pathological processes,** consisting of **tissue-degenerations and tissue-proliferations,** and of **exudations from the blood-vessels.** *Degenerations of tissue and pathological exudations initiate the process; with these tissue-proliferation is sooner or later associated,* the latter leading in the further course of the process to *compensation for the disturbance* — that is, to *healing.* The *proliferation of tissue* may, therefore, be regarded as *regenerative,* but such new-formation of tissue may be in excess of that which is useful to the body. The tissue-degenerations and proliferative processes described in the previous chapters appear for the greater part as participating factors in inflammation; the inflammatory *process acquiring its character through the combination of tissue-degenerations and tissue-proliferations with pathological exudations.*

Injury of tissues containing blood-vessels produces changes which constantly bear at some time during their course the character of an inflammation. The formation of scar tissue, the healing of transplanted tissues, as briefly described in the last chapter, *always take place through processes that are essentially inflammatory in nature.*

Exudation in acute inflammation is constantly associated with *hyperæmia,* which appears even before the beginning of exudation, and hence ushers in the latter. As a result of the combination of hyperæmia and exudation the inflamed tissue becomes reddened and swollen. When situated on the surface of the body the increased flow of warm blood from the deeper tissues causes local increase of temperature. If the inflamed tissue contains sensory nerves, pain will be produced as the result of the mechanical effects of the exudate.

Redness, swelling, increased warmth, and **pain** are phenomena which even in ancient times were regarded as the signs of inflammation; **rubor, tumor, calor,** and **dolor** were designated by Celsus the **cardinal symptoms of inflammation.** To these four was then added a further symptom, **functio læsa, altered function** of the inflamed tissue.

The **causes of inflammation** lie in *mechanical, thermal, bacterial, electrical,* or *chemical* influences. The common characteristic of all these injurious agencies is *the production, in the first place, of local tissue-degeneration, which, when of a certain extent* and *intensity, is associated with disturbances of the circulation and exudation from the vessels.* The causes of inflammation are not specific; any injurious agent may excite inflammation if its action is sufficiently intense to cause certain disturbances of circulation in association with tissue-degenerations, but not so intense as to destroy the tissue and stop the circulation.

The majority of the causes of inflammation reach the body from the outside, but excitants of inflammation may be formed within the body.

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Bacteria which have penetrated into the tissues often form in their protoplasm or from substances present in the body products which are capable of exciting inflammation. Moreover, substances that excite inflammation may arise in the organism without the aid of parasites; particularly as the result of the death of large masses of tissue from any cause, or when in metabolic processes abnormal products are deposited in the tissues.

The causes of inflammation may act on the tissues from portions of the body accessible from without, or from the lymph and the blood; and we may, therefore, distinguish **ectogenous, lymphogenous,** and **hæmatogenous inflammations.** Through the spread of inflammation to neighboring tissues there arises **inflammation by continuity;** as the result of transportation through the lymph or blood stream of an agent causing inflammation, there are produced **metastatic inflammations.** If injurious substances are discharged through the excretory organs, **excretory inflammations** may arise.

When local injury to tissues has reached such a degree as to produce the exudation characteristic of inflammation, there is an associated **hyperæmia,** as a result of which the blood flows through the dilated vessels with increased velocity. After a short time, lessening of the speed of the circulation leads to abnormal **slowing of the current.**

The **disturbances of circulation,** which find expression in hyperæmia, may be due to stimulation or paralysis of the vasomotor system or to direct action on the vessel-walls, particularly the arterial walls, leading to dilatation of the lumen. Although these disturbances frequently precede the inflammatory exudation, they do not belong exclusively to the process of inflammation, but often occur without being followed by inflammatory exudation. Further, they may be absent during the course of an inflammation. The circulatory disturbances characteristic of inflammation are shown only when **slowing of the blood-current and exudation from the blood-vessels** set in. Slowing of the bloodstream and exudation are dependent on a *change in structure,* **an alteration of the vascular walls,** through which there results lasting dilatation of the vessel and adhesion of the blood to the vessel-wall, causing *increase of frictional resistance* and *increased permeability* of the vessel-wall. In the capillaries the persistent dilatation is in part the result of *relaxation of the connective tissue surrounding the capillaries,* inasmuch as the thinness of the capillary walls makes this tissue bear the greater part of the blood-pressure resting upon them.

The **tissue-lesion** which leads to disturbances of circulation and exudation usually affects all parts, but under certain conditions may be limited to the vessel-wall, particularly in hæmatogenous inflammation, in which the injurious agent acts from the blood. However, the tissue adjoining the capillary walls must soon become involved. The tissue-changes brought about by the excitants of inflammation are sometimes slight, and even on microscopic examination are not recognizable at all or with difficulty; at other times they are so severe that they may be easily recognized on macroscopic examination. The latter is particularly true when some time has elapsed after the action of the injurious agent. During the further course of the inflammatory process there are often added to the lesions produced directly by the causes of inflammation other tissue-changes, which are brought about by disturbances of circulation and the collection of exudate in the tissues.

If in any tissue the cause of inflammation has led to that alteration of the vessels which is the requisite antecedent for the formation of an exudate, and if as a result of this alteration there is slowing of the blood-stream, the capillary circulation becomes irregular, due either to complete or transitory stasis in different areas. In this event the white blood-corpuscles often remain clinging to the vessel-walls while the red blood-cells are carried on, and there arises in the capillaries a more or less marked increase of white blood-corpuscles as compared to the red.
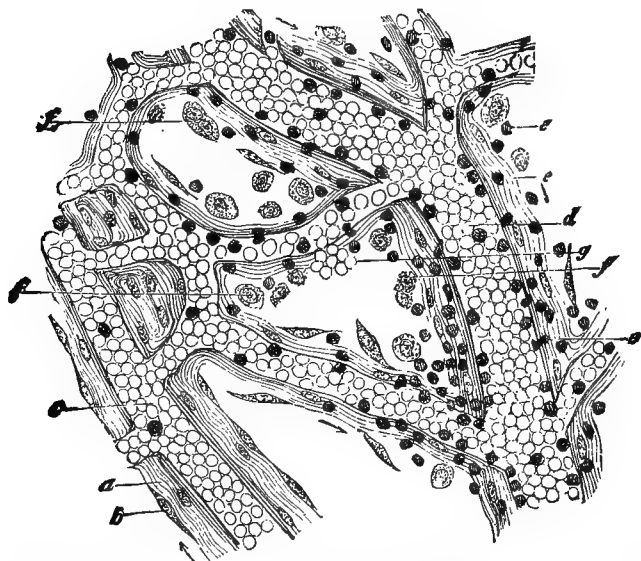
FIG. 163.—Inflamed human mesentery (osmic-acid preparation). *a*, Normal trabecula; *b*, normal epithelium (endothelium); *c*, small artery; *d*, vein with leucocytes arranged peripherally; *e*, white blood-cells which have emigrated or are emigrating; *f*, desquamating endothelium; *f₁*, multinuclear cells; *g*, extravasated red blood-cells. × 180.

In the veins, in which there can be distinguished in the normal circulation an axial red stream and a peripheral plasma-zone free from cells, greater or less numbers of **leucocytes pass over into the plasma-zone,** when the slowing of the circulation has reached a certain degree. Still greater slowing of the current leads to the passing over of blood-plates and red cells, and finally the distinction between axial-stream and peripheral zone may be entirely lost.

When leucocytes pass over into the peripheral zone they either roll along or cling to the wall of the vein, either to roll on again or to remain attached. If this leads to marked accumulation of leucocytes along the vein-walls, the condition is known as **marginal disposition of white corpuscles** (Fig. 163, *d*).

Following the accumulation of the leucocytes in the capillaries and the marginal disposition in the veins there occurs *emigration of leucocytes* (Fig. 163, *d, e*) from the vessels involved, and at the same time fluid escapes *from the vessels into the tissues*.

The **emigration of white corpuscles** is an active process, and is accomplished through the amœboid movement of the cells; to a certain extent it occurs under normal conditions. The cause of the marked emi-

gration seen in inflammations is doubtless a change in the vessel-walls, which favors the clinging of the cells to the walls and their passage through the latter. According to investigations by Arnold, Thoma, and others, the leucocytes pass out through the lines of cement-substance between the endothelial cells; and in the alteration of the vessel-wall due to inflammation localized defects occur as the result of widening of these lines. The emigration is accomplished by the leucocytes sending a process through the vessel-wall, the remainder of the cell-body flowing after the process, until finally the entire cell is outside the vessel. Arrived here the leucocytes remain for a while in the immediate neighborhood of the point of diapedesis, but then wander farther, the direction being determined partly by *mechanical stimuli*, partly by *chemotaxis* — that is, the repulsion or attraction exerted by chemical substances in the tissue-juices. Possibly chemotactic influences exert an action even on the leucocytes in the capillaries or in the peripheral zone of the veins. The cells emigrating from the vessels are almost exclusively *polynuclear leucocytes*, but *lymphocytes* may accompany them. Polynuclear leucocytes, passing out in great numbers and accumulating in the adjacent tissues, are known as *pus cells*..

The **pouring-out of fluid exudate,** whose composition differs more or less from that of normal tissue-lymph, and is characterized by a *relatively high albumin-content*, is a process also to be referred to *alteration of the vessel-wall*. It takes place at the same time as the emigration of leucocytes, but may begin before this event, and may also occur in cases in which the emigration of leucocytes does not take place at all, or remains within narrow limits. The *composition of the exudate* varies, but it may be assumed that the albumin-content is higher the greater the damage to the vessel-walls. If the extravasated fluid contains fibrinogenic substances separation of fibrin and coagulation occur.

If the alteration of the vessels is of high degree, or if at the same time there is marked stasis, **red blood-cells may pass out of the vessels** (Fig. 163, *g*) with the fluid, either by rhexis or diapedesis. According to Thoma and Engelmann rhexis of red cells occurs particularly in those places where leucocytes have previously passed through the vessel-wall. Since red cells are not motile, their escape must be regarded as a passive process performed under the influence of pressure.

The **escape of blood-plates** may take place both in exudates rich in cells and those containing few, but occurs particularly in exudates with an abundance of fibrin and red blood-cells.

Tissue-proliferation — that is, division of cells and nuclei — is first recognizable about eight hours after the action of the injurious agent; and in many cases appears later. In other words, tissue degeneration and exudation from the vessels precede proliferation, assuming, of course, that the inflammation does not arise in a tissue which is already in a state of proliferation.

The clinical significance of the term *inflammation* (*inflammatio, phlogosis*) has changed but little in the course of time, since the cardinal symptoms of inflammation set forth by Celsus, and accepted by Galen, are recognized as such at the present day. Nevertheless, the views regarding the differentiation of the essential from the unessential in the symptom-complex of inflammation and the accurate determination of the true nature of the process have differed greatly. A comparison of the expressions concerning these points made by the more modern writers (*Virchow, von Recklinghausen, Cohnheim, Ponfick, Samuel, Thoma, Neumann, Stricker,*

Heitzmann, Grawitz, Leber, Metschnikoff, and others) shows that no single writer defines inflammation in the same way as any other, or interprets in exactly the same way any one of the individual phenomena of inflammation. *Ponfick* designates as the cause of inflammation the disturbance of equilibrium in the tissues, "but hesitates to designate retrogressive changes as an indispensable attribute of the inflammatory process, and doubts wholly that they should be regarded as the point of departure and the chief feature of the process." I am of the opinion that "a disturbance of the tissue-equilibrium" is nothing more than a degenerative change of tissue, and regard *Ponfick's* statement, though directed against my definition, as harmonizing with my views. Moreover, I once again emphasize the fact that the alteration of the vessels is a necessary requisite for exudation, and that this alteration is nothing else than a tissue-degeneration.

It was formerly believed that hyperæmia was the essential symptom of inflammation. *Rokitansky* held that every inflammation was characterized by dilatation of the capillaries, slowing of the blood-stream, and by stasis caused by thickening of the blood through the effusion of serum and adhesion of the red blood-cells to one another. *Henle, Stilling,* and *Rokitansky* attributed dilatation of the vessels and slowing of the circulation to paralysis of the nerves of the vessels, the cause of which, according to *Henle* and *Rokitansky,* is increased stimulation of the sensory nerves; while according to *Stilling,* the cause lies in paralysis due to the inflammatory irritant. *Eisemann, Heine,* and *Brücke* sought to attribute the circulatory disturbances to primary spasm of the vessels brought about by irritation of sensory nerves, which produces behind the contracted portions of the vessels slowing of the current, irregular circulation, and finally stasis. *Vogel, Emmert, Paget,* and others, on the other hand, attributed dilatation of the vessels and stasis to abnormal attraction of the blood by the tissues. Against these views it must be maintained that the disturbances of circulation produced by contraction or dilatation of the vessels introduce or accompany those leading to exudation, and may exert a modifying influence on the course of inflammation, but do not form an essential part of the process, and may be entirely wanting, or may appear without the accompaniment of an inflammatory exudate.

The recognition that the formation of the exudate is to be referred to injury of the vessel-walls we owe chiefly to *Cohnheim,* whose investigations were completed by *Samuel, Arnold, Thoma, Binz,* and others. *Cohnheim* also showed that in inflammation the colorless corpuscles emigrate, and form an essential constituent of the exudate.

Dutrochet ("Rech. anatomiques et physiologiques sur la structure interne des animaux et des végétaux et sur leur motilité," Paris, 1842, p. 214) and *Waller* (*Philosoph. Magaz.,* xxix., 1846, pp. 271, 398) as early as 1842 and 1846, respectively, described the escape of colorless corpuscles from the blood-vessels. These observations had, however, fallen into oblivion until *Cohnheim,* in 1867, rediscovered the phenomenon.

According to researches of *Schklarewsky* (*Pflüger's Arch.,* Bd. i.), the peripheral disposition of the leucocytes in the veins is purely a physical phenomenon. If fluids, in which are suspended finely powdered substances of different specific gravity, are made to flow through tubes, it will be found that at a certain degree of retardation of the current, the bodies of lighter specific gravity pass over into the peripheral zone and at a more marked retardation the heavier bodies also enter this zone.

For the emigration of the white corpuscles, it is necessary, according to *Binz, Thoma,* and *Lavdowsky,* that they be capable of motion and of adhering to the vessel-wall. According to these observers, the emigration of the white blood-cells is not a passive, but an active process. If the amœboid power of the white cells be lessened by means of irrigation of the mesentery with a 1.5-per-cent. solution of salt (*Thoma*), or if the energy of these cells be lowered by means of quinine or iodoform (*Binz, Appert, Kerner*), there results inhibition of emigration. On the other hand, *Pekelharing* believes that quinine, oil of eucalyptus, and salicylic acid cause contraction of the veins, lessen the permeability of their walls, and thereby hinder the passing-out of white cells. This view is rejected, however, by *Disselhorst,* who observed dilatation of the veins after irrigation of the tissues with quinine, carbolic acid, salicylic acid, and mercuric chloride. As there occurs in this case retardation of the current after transitory acceleration, without emigration of the leucocytes collected in the peripheral zone; and as, on the other hand, leucocytes from blood-vessels that have been irrigated for an hour with quinine still retain complete vitality (*Eberth*), *Disselhorst* is of the opinion that the drugs

mentioned so change the inflamed vessel-wall that adhesion of the leucocytes rolling along the wall either cannot occur at all or only with difficulty.

It is probable that a lesion of the vessel-wall is not necessary for the emigration of leucocytes (*Thoma*). Since vasomotor disturbances of circulation can produce migration (*von Recklinghausen, Thoma*), it is probable that all conditions necessary for this process are furnished by slowing of the blood-stream with peripheral disposition of the colorless corpuscles and the ability of the leucocytes to perform amœboid movements and to adhere to the vessel-walls. It is possible that differences in the water-content of the tissues (*Thoma*) exert some influence, since an increased amount of water causes increased amœboid movement. It is also possible that the presence in the tissue-fluids, of substances having active chemo-
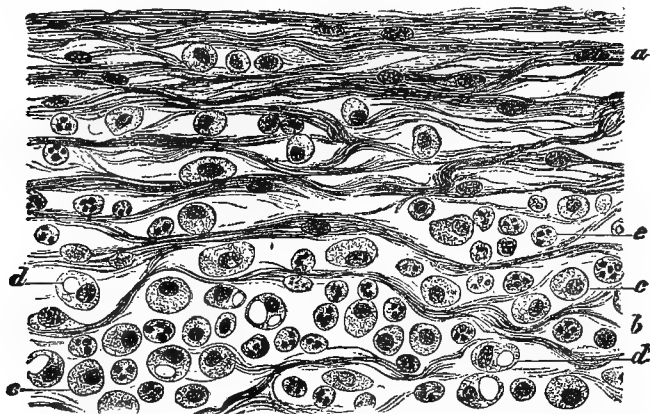
FIG. 164.—Recent purulent meningitis (Müller's fluid, hæmatoxylin). *a*, Arachnoid; *b*, subarachnoideal tissue; *c, d*, desquamated endothelium; *e*, pus-corpuscles. × 300.

tactic properties causes emigration of those leucocytes in the peripheral zone that are adherent to the vessel-wall.

According to the investigations of *Arnold, Thoma,* and *Engelmann*, there is present between the edges of the endothelial cells a soft cement-substance which suffers a change in the circulatory disturbance associated with cell-migration. This change may sometimes, but not always (*Löwit*), be recognized, on histological examination, in the form of numerous circumscribed widenings of these intercellular areas (*Engelmann*). If leucocytes pass through these places in great numbers the cement-substance becomes still more permeable, and lymphocytes and red cells escape in rapid succession (*Thoma*).

The inflammatory disturbances of circulation and the formation of exudates may be most easily followed in the transparent membranes of cold-blooded animals, particularly in the mesentery, or the extended tongue or web of the frog. In the frog's mesentery, which has been spread out on a suitable glass plate, circulatory disturbances and inflammation develop simply through exposure to the air and the resulting evaporation; in the case of the tongue and web, it is necessary to cauterize in order to produce inflammation. By the employment of suitable apparatus the circulation of the blood and the formation of the inflammatory exudate may also be observed under the microscope in the thin membranes of mammals (mesentery of rabbit, wing-membrane of bat), and observations thus made harmonize wholly with those made on the frog.

The modern conception of inflammation is that it is a *pathological complex essentially adaptive, protective, and reparative, called into action by a primary tissue-lesion*. For a presentation of this view see *Warthin*, Chapter on Inflammation, "American Practice of Surgery," Vol. I.

§ 90. The *cellular and fluid exudate* from the vessels collects first in the immediate neighborhood (Fig. 164, *e*), but soon spreads in the *lymph-spaces* and thus forms a **tissue-infiltrate** (Figs. 165, *b;* 168, *p*).

When the exudate is abundant it may infiltrate tissue that has not been injured by the inflammatory irritant. This **infiltration** may be so marked
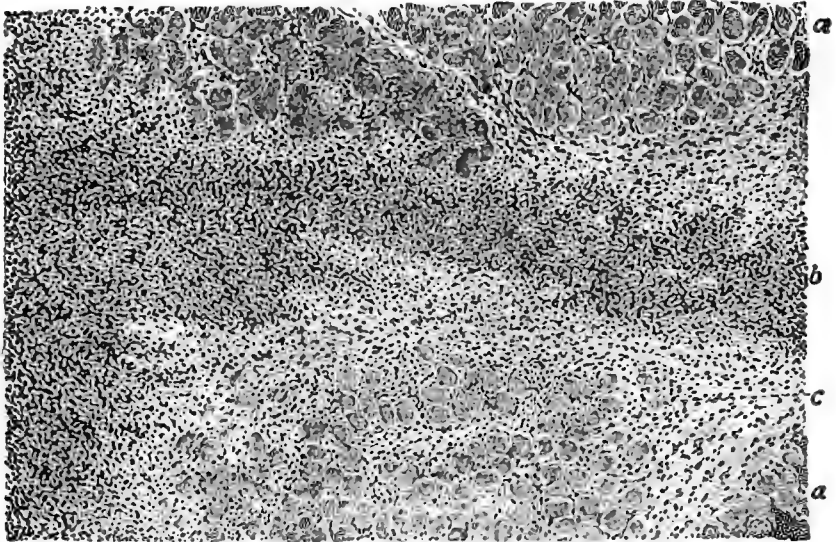
FIG. 165.—Hæmatogenous staphylococcus myositis (alcohol, hæmatoxylin-eosin). *a*, Transversely cut muscle-bundles; *b*, purulent; *c*, seropurulent, partly coagulated exudate.   × 45.
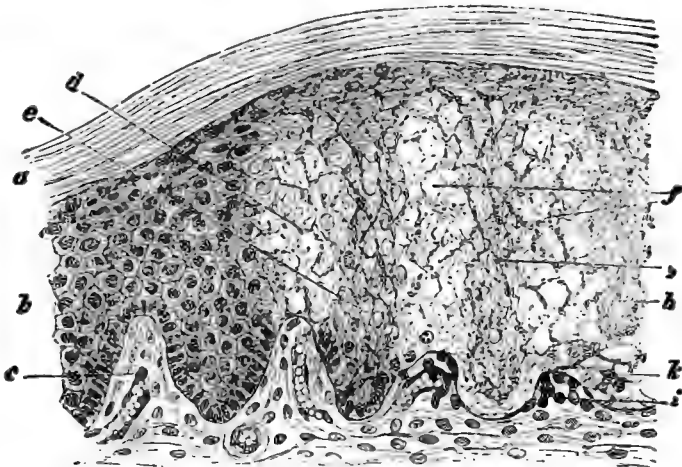
FIG. 166.—Section through the border of a blister caused by a burn (alcohol, carmine). *a*, Horny layer; *b*, rete Malpighii; *c*, normal papillæ; *d*, swollen cells, some of whose nuclei are still visible though pale, while others have been destroyed; *e*, interpapillary epithelial cells, the deeper ones intact, those of the upper layers are drawn out longitudinally and in part are swollen and have lost their nuclei; *f*, total liquefaction of the cells; *g*, interpapillary cells, without nuclei, swollen and raised from the cutis; *h*, total degeneration of interpapillary cells which have been raised from the cutis; *k*, coagulated exudate (fibrin) lying beneath the uplifted epithelium; *i*, flattened papillæ infiltrated with cells.   × 150.

that new disturbances of circulation and nutrition are produced, and the *area of tissue-degeneration and inflammatory exudation becomes increased in extent.*

The *fluid exudate may be partly absorbed by the tissue-elements*, so that they become swollen, separated from their surroundings (Fig. 164, *c*, *d*), and contain *drops of fluid* (*d*) which are commonly designated *vacuoles*.
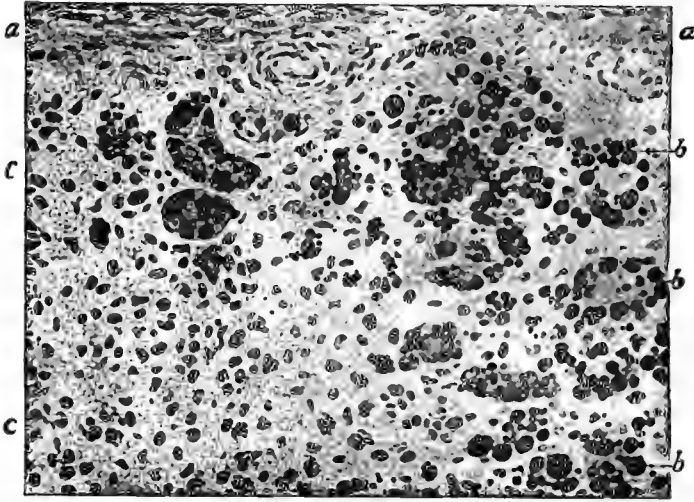
FIG. 167.—Parenchymatous hepatitis (Flemming's solution, safranin). *a* Liver-capsule; *b*, liver-rods showing fatty degeneration; *c*, liver-cells showing total degeneration × 300.
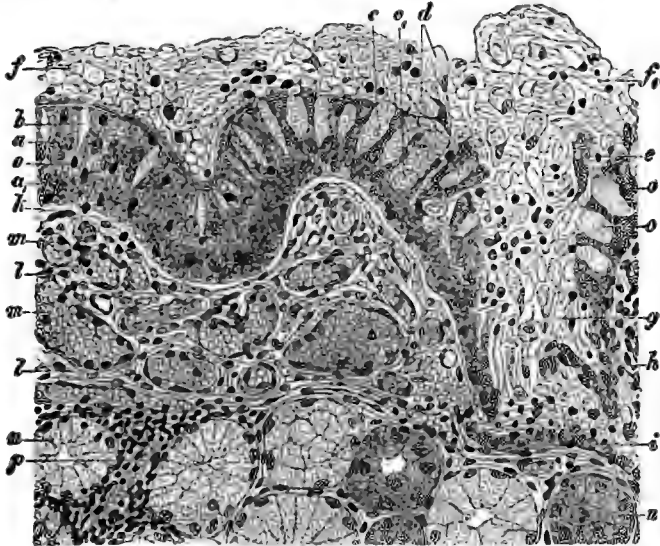
FIG. 168.—Mucous catarrh of a bronchus (Müller's fluid, aniline-brown). *a*, Ciliated epithelium; *a₁*, deeper cell-layers; *b*, goblet-cells; *c*, cells showing marked mucous degeneration; *c₁*, mucoid cells with mucoid nuclei; *d*, desquamated mucoid cells; *e*, desquamated ciliated cells; *f*, layers of drops of mucus; *f₁*, layer consisting of thready mucus and pus-corpuscles; *g*, duct of mucous gland filled with mucus and cells; *h*, desquamated epithelium of the excretory duct; *i*, intact epithelium of the duct; *k*, swollen hyaline basement-membrane; *l*, connective tissue of the mucosa, infiltrated with cells in part; *m*, dilated blood-vessels; *n*, mucous gland filled with mucus; *n₁*, lobule of mucous gland without mucus; *o*, wandering cells in epithelium; *p*, cellular infiltration of the connective tissue of the mucous glands. × 110.

There also occurs **solution of tissue-elements** in the exudate (Fig. 166, *d*, *f*) and of connective tissue cells, and intercellular substances. In this way brain and muscle tissue, as well as ordinary connective tissue, which have been killed as the result of injury, may become completely liquefied in the course of inflammation.

If dead cells become saturated with lymph containing fibrinogen, and if fibrin-ferment is formed, the liquefaction of the infiltrated tissue may be preceded by **coagulation,** and the cells become changed into homogeneous masses without nuclei, or partly into granular and fibrillar masses.

If the exudate — for example, in a muscle — lies in the supporting tissue, while the parenchyma suffers but little change, the inflammation is designated **interstitial inflammation** (Fig. 165, *b*). If, on the other hand, degeneration of the parenchyma — e.g., the epithelium of the kidney tubules, the liver-cells (Fig. 167, *b*, *c*), or the contractile substance of muscles — is the most prominent feature of the process, the condition is called **parenchymatous inflammation.**

When the seat of inflammation is the surface of an organ it is termed **superficial inflammation** (Fig. 168). If the exudate gains access to the surface and escapes mixed with desquamated portions of tissue (Fig. 168, *d*, *e*, *f*, *f₁*, *g*, *h*), the inflammation is called catarrh. If the pouring out of fluid exudate on the surface of skin or mucous membrane is hindered by

Fig. 169.—Purulent desquamative catarrh of the trachea in measles (alcohol, hæmatoxylin, eosin). *a,* Layer of pus-corpuscles and desquamated epithelium; *b,* intact deepest layer of epithelium; *c,* basement-membrane; *d,* hyperæmic and infiltrated connective tissue of the mucosa; *e,* infiltrated submucosa with mucous glands. × 100.

a horny epithelial layer (Fig. 166, *a*), and if beneath this there are circumscribed collections of fluid, in which the deeper and softer layers of the epithelium dissolve (Fig. 166, *d, f, g, h*), the lesions produced are called **vesicles** and **blisters.** The exudate from serous surfaces collecting in the body cavities are termed **inflammatory effusions,** and may reach such size as to distend the affected cavity and compress the organs contained in it.

It is customary to express the occurrence of inflammation by adding the termination *"itis"* to the Greek name of the organ. Thus are formed the terms endocarditis, myocarditis, pericarditis, pleuritis, peritonitis. encephalitis, pharyngitis, keratitis, orchitis, oöphoritis, colpitis, metritis, hepatitis, nephritis, amygdalitis, glossitis, and gastritis. The ending *" itis "* is sometimes affixed to the Latin names, for example, conjuctivitis, tonsillitis, vaginitis, etc. To denote inflammation of the serous covering of an organ or of the tissues immediately about it the prefixes *" peri "*
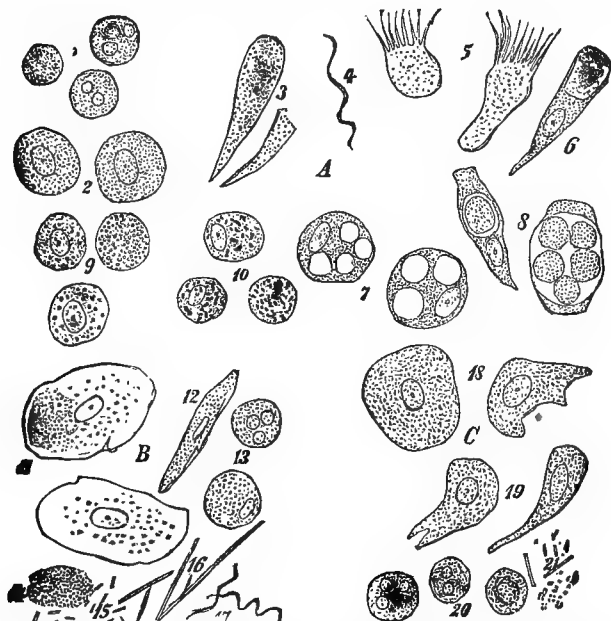
Fig. 170.—Caharrhal secretion of different mucous membranes. *A,* Secretion from mucous membranes with columnar cells; *B,* from the mouth; *C,* from the bladder. 1, Round cells (pus-cells); 2, large round cells with bright nuclei, from the nose; 3, mucoid columnar cells from the nose; 4, spirillum from the nose; 5, mucoid cells with cilia, from the nose; 6, goblet-cells from the trachea; 7, round-cells with spherules of mucus from the nose; 8, epithelial cells containing pus-corpuscles, from the nose; 9, fatty cells from a chronic catarrh of the pharynx and larynx; 10, cells containing carbon pigment, from the sputum; 11 and 12, squamous epithelium from the mouth; 13, mucoid pus-corpuscles; 14, micrococci; 15 bacteria; 16, *leptothrix buccalis;* 17, *spirochaete denticola;* 18, superficial, 19, middle layer of bladder epithelium; 20, pus-corpuscles; 21, *schizomycetes.* × 400.

and *" para "* are placed before the Greek names with the termination *" itis."* Thus are formed the words perimetritis, parametritis, periproctitis, paranephritis, perihepatitis, etc.

For certain forms of inflammation special names are used, for example, inflammation of the lungs is called pneumonia, and inflammation of the palate and tonsillar regions, angina.

§ 91. *Local tissue-degeneration* and *exudation* vary in different cases, and there may accordingly be distinguished different **forms of inflammation.**

If the exudate consists essentially of fluid, while the cellular constituents are insignificant, it is called a **serous exudate;** circumscribed collections of clear fluid beneath the horny layer of the epidermis with liquefaction of the soft layers of the epithelium lead to the formation of **vesicles** and **blisters** (Fig. 166, *d, f*).

When the exudation of fluid on a mucous membrane is associated with mucoid degeneration of the surface epithelium (Fig. 168, *b, c, c₁*), and of the mucous glands (*n*), the con-dition is termed **mucous catarrh** (*d, f, f₁, g*). If marked desquamation of the epithelium, with or without mucoid change, occurs (Fig. 169, *a*), the condition is termed **desquamative catarrh**; such a process may occur not only on mucous membranes, but also in the air vesicles of the lungs, in the kidney-tubules, etc. If pus-corpuscles are present in the exudate it may be spoken of as **purulent catarrh**; in which condition the exudate becomes white or yellowish-white, milky or creamy.

The form and character of the cells of a catarrhal secretion vary with the location and the variety of catarrh (Fig. 170). Bacteria are often present in the cells of the exudate (Fig. 170, *4, 14, 15, 16, 17, 21*).

If in a fluid exudate there is depo-sition of fibrin, **serofibrinous exu-dates** are formed, and are often desig-nated **croupous**. These occur chiefly on the surface of serous and mucous membranes, and in the lungs; but masses of fibrin may be formed in tissues infiltrated with exudate, as well as in lymph-vessels.

On mucous membranes fibrinous

Fig. 171.—Acute hæmorrhagic fibrinous inflammation of the trachea, caused by vapor of ammonia (Müller's fluid, hæma-toxylin, eosin). *a,* Superficial layer of the connective tissue of the mucosa, with greatly dilated blood-vessels and extrava-sated red blood-cells; *b,* deep layer of epi-thelium raised up *in toto; c,* desquamated epithelial cells; *d,* hæmorrhagic fibrinous exudate with radiating, crystal-like masses of fibrin, in part proceeding from small, colorless spherules. × 300.

exudates form whitish patches, which sometimes lie loosely, at other times are attached. In the serous cavities fibrinous coagula float in the fluid portion of the exudate, or are de-posited on the surface. Such deposits consist of thin films or gran-ules which give to the surface a cloudy, lustreless, rough, or granular appearance; or of larger yellowish or yellowish-red, firm membranes, which im-part a felted or villous appearance (cor vil-losum). In the lung,

Fig. 172.—Croupous membrane from the trachea. *a,* Section through membrane; *b,* uppermost layer of the mucosa in-filtrated with pus-corpuscles (*d*); *c,* fibrin threads and granules; *d,* pus-corpuscles. × 250.

croupous inflammation leads to filling of the alveoli with a coagulated mass, in consequence of which the lung acquires a firm consistence.

On *mucous surfaces* the formation of croupous membranes takes place when the epithelium is desquamated and the connective tissue, at least in part, is exposed; but tissues covered with epithelium may become the seat of fibrinous deposits extending from denuded areas. The desquamation of epithelium may follow gradually, at other times rapidly through
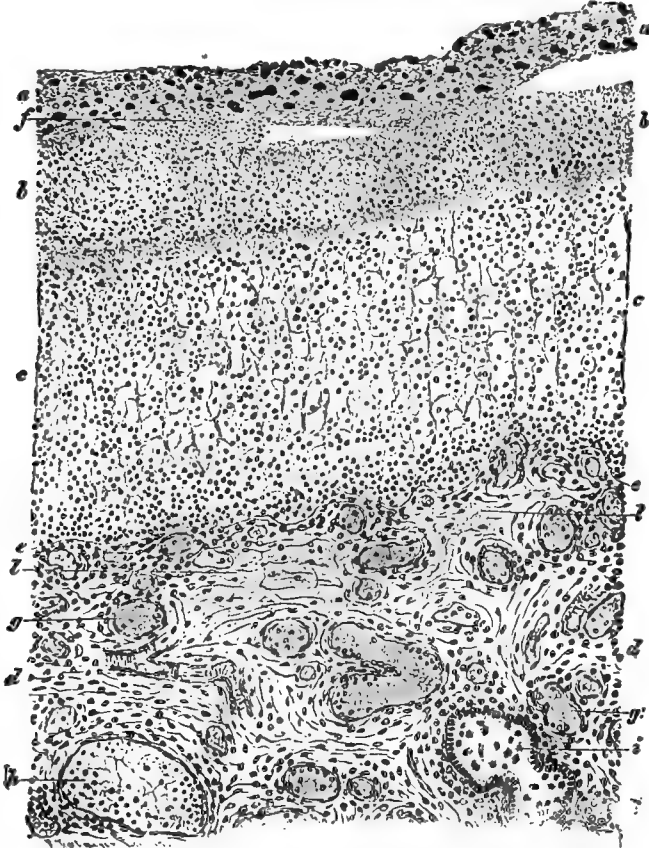
FIG. 173.—Section from an inflamed uvula covered with a stratified fibrinous membrane, from a case of diphtheritic croup of the pharyngeal organs (Müller's fluid, hæmatoxylin, eosin). *a*, Surface layer of coagulum, consisting of epithelial plates and fibrin and containing numerous colonies of cocci; *b*, second layer of coagulum, consisting of fine-meshed fibrin network enclosing leucocytes; *c*, third layer of coagulum, lying upon the connective tissue, consisting of a wide-meshed reticulum of fibrin enclosing leucocytes; *d*, connective tissue infiltrated with cells; *e*, infiltrated boundary layer of the connective tissue of the mucous membrane; *f*, heaps of red blood-cells; *g*, widely dilated blood-vessels; *h*, dilated lymph-vessels filled with fluid, fibrin and leucocytes; *i*, duct of a mucous gland distended with secretion; *k*, transverse section of a gland; *l*, fibrin reticulum in the superficial layer of connective tissue. × 45.

the lifting up of whole layers of epithelium (Fig. 171, *b*), which are either well preserved or degenerate or necrotic, and infiltrated with exudate (Fig. 173, *a*).

The deposition of fibrin may begin under the raised epithelium with the formation of fine needle-like forms (Fig. 171, *d*) ranged radially about a centre, in which at times there lies a small body, or blood-plate. Soon there form threads (Figs. 172, *c*; 173, *b*, *c*) which enclose variable numbers

of leucocytes and red cells. The arrangement of the threads is usually reticular, but the thickness of the network and the size of the meshes vary. When there is unequal development of the fibrin threads, the principal strands sometimes lie parallel with the surface of the mucous membrane (Fig. 172, *c*), sometimes perpendicular to it (Fig. 173, *c*). Thick fibrinous membranes frequently show distinct stratification (Fig. 173, *a*, *b*, *c*), indicating that their formation has occurred in successive layers.

When a mucous membrance becomes the seat of fibrin deposit, the un-
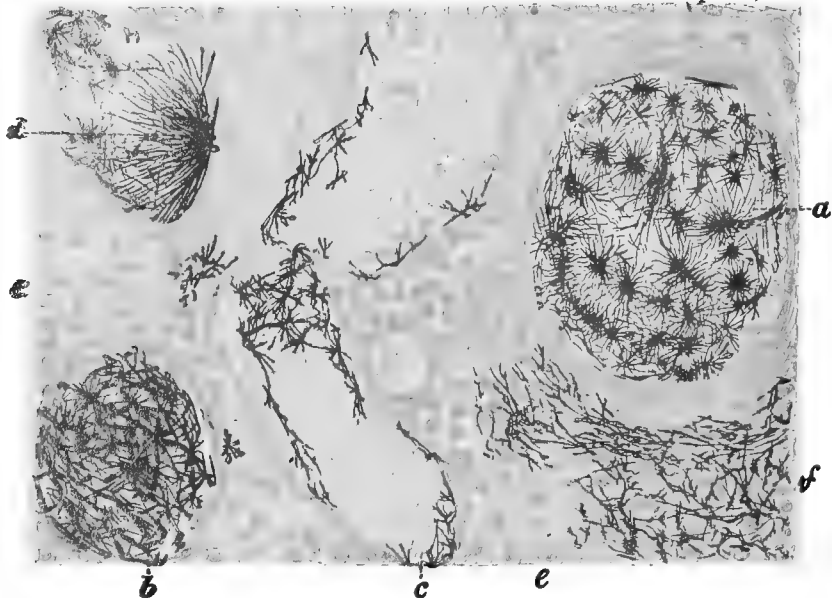
Fig. 174.—Croupous tracheitis. Section through the connective tissue of the mucosa (carmine and fibrin-stain. *a, b, c, d,* Blood-vessels with fibrin precipitates; *e,* œdematously swollen connective tissue with leucocytes; *f,* connective tissue with fibrin-threads. × 500.

derlying connective tissue is more or less hyperæmic (Fig. 173, *g*), œdematous and swollen, infiltrated with leucocytes (Figs. 173, *d, e;* 174, *e*), and usually contains thready fibrin precipitates (Figs. 173, *l;* 174, *f*). Often the tendency to precipitation of fibrin is manifested in the blood-vessels (Fig. 174), at times these contain tangled threads and rods (Fig. 174, *b*), at other times fibrin-needles grouped in stellate forms or clusters (*a, c, d*), which proceed from blood-plates, or radiate from portions of the vessel-wall where the endothelium is lost. Likewise, fibrin-threads may be found in dilated lymph-vessels, in association with fluid and cellular exudate (Fig. 173, *h*).

On *serous membranes* deposits of fibrin appear in granular and thready, or in thick, homogeneous masses, or even in the form of ribbon-like bands. Here also the epithelium is exfoliated at the point of deposition or preserved in patches and covered with fibrin. The connective tissue of serous membranes in croupous inflammation is more or less infiltrated, and may contain leucocytes and fibrin, both in the congested vessels and in the connective-tissue spaces (Fig. 175, *c*). More marked exudations on serous membranes produce thick, felted deposits, the elements of which consist of thready fibrin and

pus corpuscles (Fig. 175, *d, e*), as well as micro-organisms (*b*). An abundance of pus corpuscles gives to the exudate a *fibrinopurulent* character, the deposits becoming whitish in color.

Fibrinous exudates in the lungs are characterized by a more or less close network of fibrin (Fig. 176, *b*), in whose meshes and in the immediate neighborhood of which lie leucocytes mingled with red blood-cells (*e*), and desquamated epithelium. In the early stages there are occasionally found globular, wreath-shaped precipitates of fibrin joined together in rows.

In the *kidneys* fibrin may occur in the form of fine threads or hyaline masses in the tubules and glomerular capsules. In *lymph nodes* fibrin-threads are formed in the lymph-channels.

Hæmorrhagic exudate — that is, an exudate containing large numbers of red cells — occurs in connection with the exudation of fibrin. The exudate of croupous pneumonia contains a larger or smaller number of red blood-cells (Fig. 176, *c*), and in fibrinous pericarditis and pleuritis great numbers of red cells may escape from the vessels. Hæmorrhagic inflammations occur not infrequently in the central nervous system, in lymph nodes, in the skin and kidneys. In the last case the blood escapes from the glomerular vessels.

Serous, fibrinous, and serofibrinous inflammations are caused by thermal and chemical influences, as well as by bacteria; but are most frequently the result of infection, particularly with the *Diplococcus pneumoniæ* (Fig. 176, *b*) and the *Bacillus diphtheriæ*. The former causes croupous inflamma-
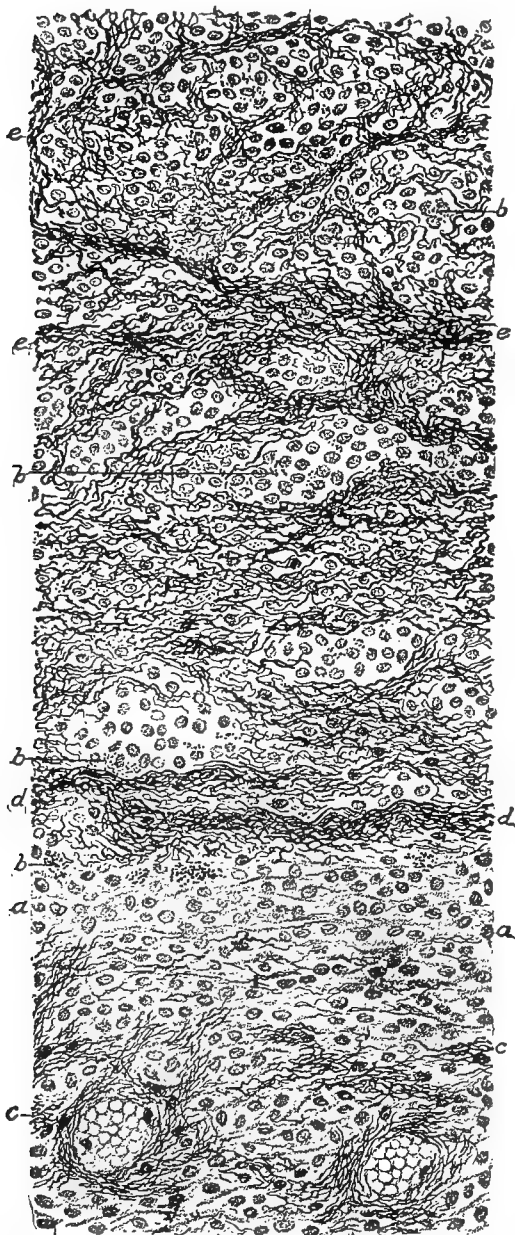
FIG. 175.—Fibrinopurulent diplococcus pleuritis in a three-year-old child (formalin, fibrin-stain). *a*, Inflamed pleura; *b*, diplococci; *c*, fibrin; *d, e*, fibrinopurulent exudate. × 500.

tions of the lungs and pleura, the latter fibrinous inflammations of the
throat, palate, and respiratory passages.
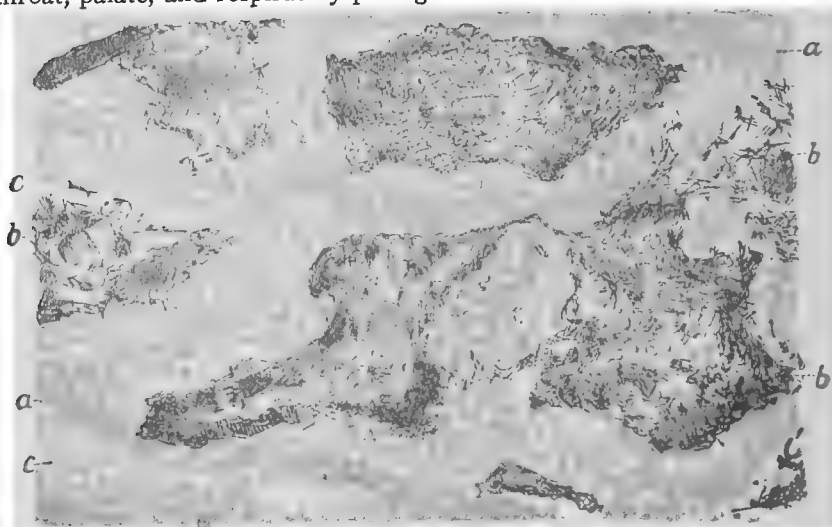
FIG. 176.—Croupous pneumonia. Red hepatization of the lung (alcohol, carmine, fibrin-stain).
a, Infiltrated alveolar septa; b, fibrinous exudate; c, red blood-cells. × 200.
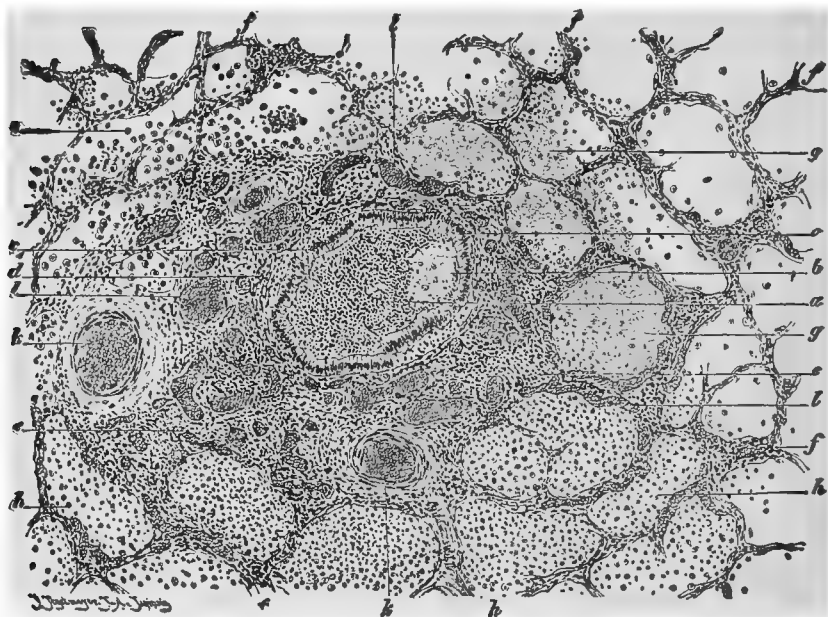
FIG. 177.—Purulent bronchitis, peribronchitis, and peribronchial bronchopneumonia in a
child one year and three months old (Müller's fluid, hæmatoxylin, eosin). a, Purulent, b, mucoid
bronchial contents; c, c1, bronchial epithelium infiltrated with round cells and partly desquamated
d, infiltrated bronchial wall with greatly dilated blood-vessels; e, infiltrated peribronchial and
periarterial connective tissue; f, alveolar septa, in part infiltrated with cells; g, fibrinous exudate
in the alveoli; h, alveoli filled with exudate rich in cells; i, alveoli filled with exudate containing
few cells; k, cross-section of a pulmonary artery; l, bronchial, peribronchial, and interacinous
vessels showing marked congestion. × 43.

§ 92. When the inflammatory exudate is made up chiefly of leuco-cytes, **infiltration** (Figs. 165, *b*; 177, *d*, *e*, *f*) may be so marked that the structure of the tissue is obscured. If *polynuclear leucocytes* or **pus-cells** are present in large numbers in the exudate on a mucous membrane or
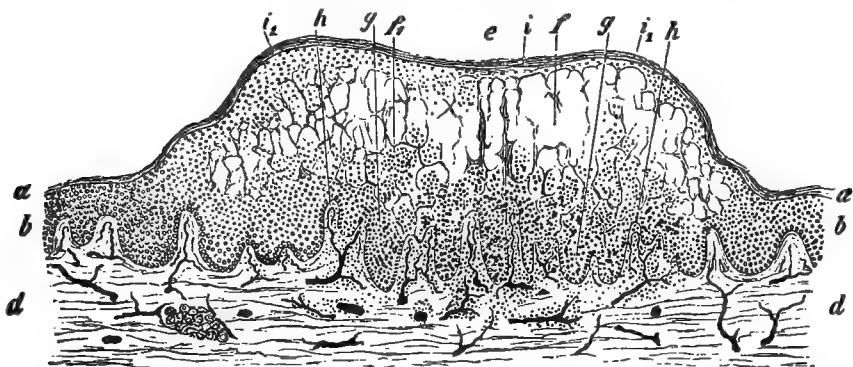
FIG. 178.—Section of a smallpox pustule (injected hæmatoxylin preparation). *a*, Horny layer; *b*, stratum mucosum of the epidermis; *d*, cutis; *e*, smallpox pustule; *f*, cavity of the pock, containing at *f₁* pus-corpuscles; *g*, interpapillary remains of epithelium infiltrated with pus-corpuscles; *h*, papillary bodies infiltrated with cells; *i*, umbilication with thin pock cover; *i₁*, edge of the pock, the roof at this point consisting of the horny and transitional layers. × 25.

wound, so that the exudate is white or yellowish-white in color and of a milky or creamy consistence, it is called **pus**; such an inflammation is designated **purulent** (Fig. 177, *a*). Persistent marked secretion is termed *blennorrhœa*. Collections of pus in the body-cavities — for example,
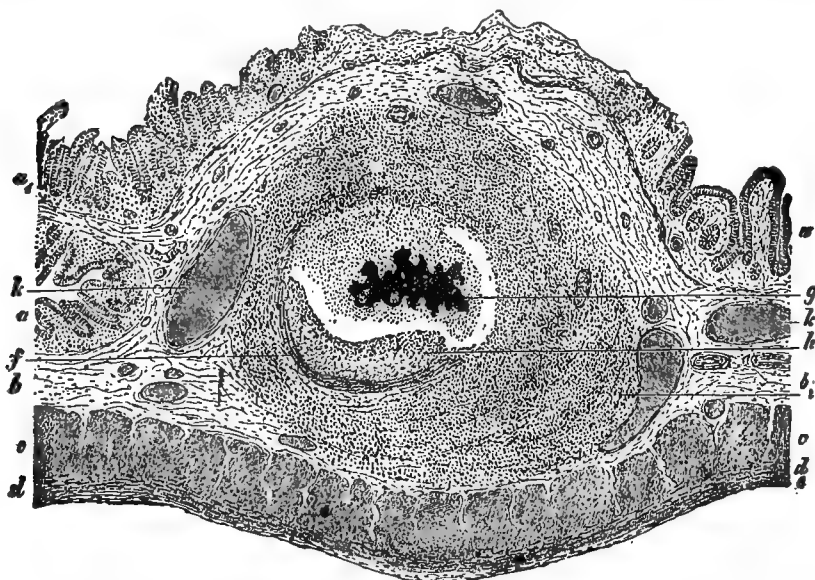
FIG. 179.—Embolic abscess of the intestinal wall with embolic purulent arteritis, and embolic aneurism in cross-section (alcohol, fuchsin). *a*, *b*, *c*, *d*, *e*, Layers of intestinal wall; *f*, remains of arterial wall, cross-section; *g*, embolus, surrounded by pus-corpuscles lying within the dilated and partly suppurating artery; *h*, parietal thrombus; *i*, periarterial purulent infiltration of the submucosa; *k*, vein showing marked congestion. × 28.

the pericardial, pleural, or joint cavities — give rise to *purulent effusions* or **empyemata.** If in a blister arising through liquefaction of epithelium below the horny layer of the epidermis there takes place marked collection of leucocytes, the fluid becomes turbid, and the vesicle is changed into a **pustule** (Fig. 178, f_1).

When leucocytes collect in a tissue in such numbers as to give it a white, gray-white, or yellowish-white color the process is known as
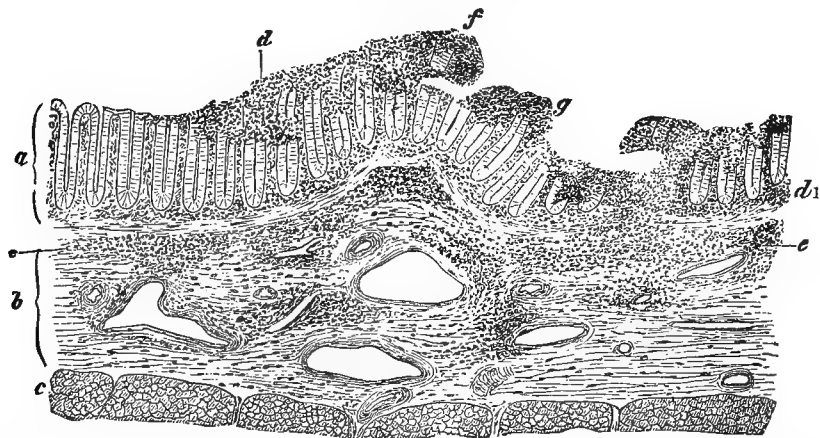
FIG. 180.—Suppuration and necrosis of the mucosa of the large intestine in dysentery (Müller's fluid, hæmatoxylin, eosin). Section through the mucosa (*a*) and submucosa (*b*) of the large intestine; *c*, muscularis; *d*, interglandular, d_1, subglandular infiltration of the mucosa; *e*, focus of infiltration in the submucosa; *f*, infiltrated upper glandular layer undergoing desquamation; *g*, ulcer with infiltrated base. ×25.

purulent infiltration. This may be followed by liquefaction and **abscess-formation** (Fig. 179, *i*)—that is, the formation of a circumscribed cavity filled with pus.

When purulent infiltration involves the superficial parts of an organ —for example, a mucous membrane (Fig. 180, *d, f, g*)—the process leads to localized loss of substance — an **ulcer.** The formation, through suppuration, of duct-like excavations gives rise to **fistulous tracts.**

If an accumulation of pus-corpuscles is associated with abundant collection of fluid, the **exudate** is spoken of as **seropurulent.** The rapid spread of purulent or seropurulent inflammation over wide areas — for example, through extensive areas of subcutaneous or submucosal tissues — is known as **phlegmon** (Fig. 181, *c, d*). This often leads to the formation of pus-cavities, in which lie shreds of disintegrating tissue infiltrated with pus.

The association of serous exudation and fibrin precipitation with suppuration leads to the formation of **fibrinopurulent exudates** (Fig. 175, *d, e*); effusions into the body-cavities, meningeal exudates, croupous exudates on mucous surfaces and in the lungs, and phlegmons may bear this character. It is to be noted, however, that with increase of suppuration the formation of fibrin becomes decreased, and coagula already present dissolve. Fibrin-masses infiltrated with pus are white and easily torn.

Suppurations and the associated formation of abscesses and ulcers are in the majority of cases caused by **bacteria**, most frequently by the

Staphylococcus pyogenes aureus, Streptococcus pyogenes, and the *Gonococcus;* but suppurations due to *Actinomyces, Bacillus anthracis, Bacillus mallei,* or the *Bacterium coli commune,* are not rare. Staphyloccoci generally produce localized inflammations; streptococci, on the other hand, phlegmonous. The presence of certain bacteria (*Bacillus phlegmones emphysematosæ,* Fränkel; *Bacillus aërogenes capsulatus,* Welch) may cause the formation of gas (*gas-phlegmon*). Suppuration is sometimes ectogenous, sometimes lymphogenous or hæmatogenous; in the last case it bears the character of an embolic process (Fig. 179).

Of the **chemical substances** which, when introduced into the tissues, produce liquefaction resembling suppuration may be mentioned mercury, oil of turpentine, petroleum, five- to ten-per-cent. solutions of silver nitrate, creolin, digitoxin, dilute croton-oil, and sterilized cultures of various bacteria, in which the bacterial proteins are the active agents. The liquefactions thus produced differ from those of infection, in that they heal more easily, do not spread in the tissues, or give rise to metastases, and their products when inoculated possess no virulence.

§ 93. Suppurative inflammation always leads to tissue-necrosis; but this necrosis is submerged in and obscured by the liquefaction and dissolution which form the characteristic feature of suppuration. In other circumstances necrosis may occur, recognizable even to the unaided eye, and is not followed by suppuration, but is characterized by the fact that the necrotic portions remain unchanged for a long time, and ultimately are removed through sequestration, sloughing, or absorption. Since necrosis in such a case forms the chief feature, the condition may be appropriately designated **necrotic inflammation.**

Fig. 181.—Phlegmon of the subcutaneous tissue with formation of a vesicle through œdema (Müller's fluid, hæmatoxylin, eosin). *a,* Corium; *b,* epidermis; *c,* infiltrated fat tissue; *d,* focus of pus; *e,* cellular foci in corium; *f,* subepithelial vesicle due to œdema. × 30.

Necrosis associated with inflammation may be caused by caustic **chemicals, high** or **low temperatures, ischæmia,** and **infection** (typhoid fever, diphtheria, dysentery, and tuberculosis).

Necrosis of tissue may appear as the immediate effect of injury, exudation following, being confined to the region adjoining the necrosis; this is especially the case after the action of corrosive substances, high temperature, and ischæmia. In other cases, inflammation is first established, the infiltrated tissue later becoming necrosed. In tuberculous

infection necrosis occurs, as a rule, after proliferation has existed for some time.

Necrotic inflammations are most frequently seen in mucous mem-
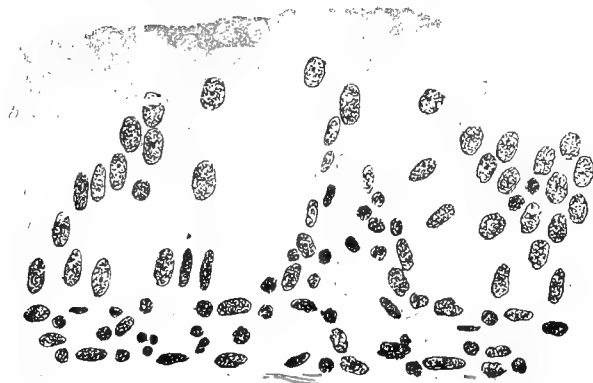
FIG. 182.—Necrosis of the epithelium of the epiglottis (Müller's fluid, hæmatoxylin). *a,* Living epithelium with well-stained nuclei; *b,* necrotic epithelium with nuclei not staining; *c,* leucocytes lying in the epithelium; *d,* hyperæmic, inflamed, and infiltrated connective tissue. × 300.

branes, and are sometimes called **diphtheritis,** particularly those caused by infection. The necrosis may first affect the epithelium, which loses its nuclei (Fig. 182, *b*) and acquires a granular appearance. If white opaque patches are formed on the mucous membrane, as in the pharynx in diphtheria, the condition may be spoken of as *epithelial* or *superficial diphtheritis.* Usually, however, the designation *diphtheritis* is applied only to necroses in which the *inflamed* and *infiltrated connective tissue* (Fig. 183, *a*), becomes converted into a granular mass without nuclei, or into a homogeneous mass containing fibrin, in which the structure of the tissue can no longer be recognized.

Diphtheritic sloughing of a mucous membrane is observed particularly often in the intestine (Fig. 183), but occurs also in the
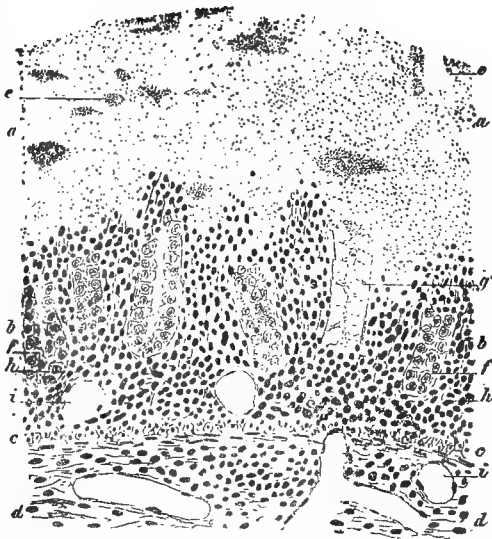
FIG. 183.—Bacillary diphtheritis of the large intestine in dysentery (alcohol, gentian violet). *a,* Necrotic portion of the glandular layer of the mucosa, infiltrated with bacilli; *b,* intact inflamed mucosa; *c,* muscularis mucosæ; *d,* submucosa; *e,* colonies of bacilli; *f,* glands with living epithelium; *g,* glands with necrotic epithelium and bacilli; *h,* connective tissue infiltrated with cells; *i,* blood-vessels. × 80.

vagina, the descending urinary passages, and the region of the throat, where the tonsils are especially affected, etc. The necrotic tissue forms white, or grayish white sloughs, which are surrounded by reddened and inflamed tissue. If some time has elapsed since its formation, and if

liquefaction at the boundary between the living and dead tissues has occurred, with separation of the latter, the necrosed parts form loosely attached or free deposits lying on the surface, consisting at times of small flakes, at other times of larger sloughs.

Diphtheritis of mucous membranes may be associated with croupous deposits (Fig. 184, c, d), so that the area of necrosis (d) may be covered with fibrin (c).
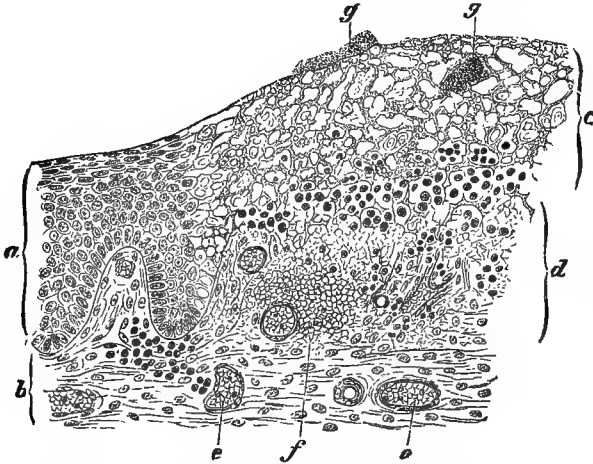
FIG. 184.—Section of the uvula in pharyngeal diphtheria with croupous deposits (alcohol, aniline brown). a, Normal epithelium; b, connective tissue of the mucous membrane; c, reticulated fibrin; d, connective tissue of mucosa infiltrated with coagulated fibrin and round cells, and partly necrotic; e, blood-vessels; f, hæmorrhage; g, clumps of micrococci. × 75.

Wound-granulations may necrose in the same way as inflamed mucous membranes; such may therefore be called *wound-diphtheritis.*

Acute tissue-necroses caused by infection occur in internal organs, notably in typhoid fever, in the lymph nodes (Fig. 185), spleen and bone-marrow, and are characterized by the formation of opaque grayish-white, yellowish, or dirty-gray sloughs. Not infrequently fibrinous collections are seen in the necrotic tissue (Figs. 184, *d;* 185).

In the necrosis caused by tuberculosis, destruction of tissue occurs gradually, and bears the character of **caseation.**

When an inflammatory focus contains bacteria which excite putrid decomposition of albuminoid bodies, the inflammation may take on the **character of putrid gangrene;** the tissue may dis-

FIG. 185.—Diphtheritic necrosis within a swollen mesenteric lymph-gland, in typhoid fever (alcohol, fibrin-stain). Fibrin network between the necrotic cells. × 300.

integrate into a dirty gray or black, tinder-like mass which gradually dissolves and gives off an extremely disagreeable odor. Gas-bubbles are sometimes developed in the focus. (See § 92.)

II. The Termination of Acute Inflammation in Healing.

§ 94. Should acute inflammation occur in any tissue, sooner or later processes arise whose object is restoration of the damaged tissue, and may therefore be regarded as **processes of repair.** These consist in the *cessation of pathological exudation* and its replacement *by normal secretions,* the *removal or absorption of exudate and of necrotic tissue,* and *restoration of destroyed tissue.* If the *exciting cause of the inflammation* is still present in the tissue and active, it must be *removed or rendered inert.*

The **repair of the vessel-walls** is brought about through restoration of the blood-supply, so that the nutrition of the vessels becomes normal. If the alteration is slight, restoration may take place in a time that may be measured in minutes and hours.

When the exciting cause of the inflammation acts at some length — as in the case of bacteria which live and multiply in the tissues, and if there
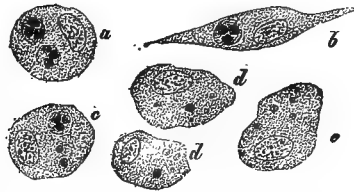
FIG. 186.—Phagocytes from granulation tissue with included leucocytes and fragments of same (sublimate, Biondi's stain). *a,* Round, *b,* spindle, fibroblast with leucocytes; *c, d, e,* fibroblasts containing remains of leucocytes. × 500.

has been, for example, necrosis of the vessel-walls, complete restoration is hindered or prevented entirely.

The **absorption of exudate** occurs in many cases easily and quickly, in that it is taken up by the lymph-stream, eventually by the blood. This takes place most rapidly in serous exudates, in many places fibrinous exudates may also be removed, but only when the coagula liquefy. For example, coagulated exudate in the lung may be liquefied and made capable of absorption through the action of a *proteolytic enzyme* (Müller) that arises most probably from the leucocytes. The absorption of exudates is often aided by **phagocytes,** that is, through amoeboid cells taking up corpuscular substances and destroying them. Thus, large mononuclear cells (macrophages) may take up polynuclear leucocytes (Fig. 186, *a, b*) and digest them (*c, d, e*). In the same manner red blood-cells and their disintegration-products may be disposed of (Fig. 96). Firmer fibrinous exudates such as are formed on serous membranes, and large collections of pus, offer considerable resistance to absorption. In many cases absorption is accomplished by the substitution for the exudate of embryonic tissue which later becomes changed into connective tissue.

The **sequestration and absorption of necrosed tissue,** with the exception of dead epithelium, which may be quickly accomplished, require a length of time which varies according to the nature, situation, and extent of the lesion. In general, inflammation persists as long as necrotic tissue is present. *Superficial necrosed tissues may be cast off after sequestration* from the living. In deep-seated necroses in which

the tissue does not undergo total liquefaction, *absorption* is slow, and is brough about through gradual substitution of living tissue for the dead. **Phagocytosis** often takes place in the absorption of necrotic tissue.

The **regeneration of tissue** in inflammatory lesions is dependent on the degree and extent of degeneration, on the nature of the tissue, and on the mode of action of the agent exciting the inflammation.

If the tissue-cells of the inflamed area are but slightly degenerated, they are quickly restored when the nutrition becomes normal. If single cells are lost but the organization of the whole is not disturbed, there can take place in certain tissues renewal of cells through regenerative growth of remaining cells. This is particularly true of different forms of connective tissue, surface epithelium, the cells of lymph nodes, etc., while ganglion-cells and heart-muscle possess little or no power of regeneration (see Chapter VI.). Extensive destruction of tissue with solution of continuity, wounds, fractures, suppuration, necrotic inflammations, etc., produce proliferations which are sufficient to close the defect, but do not lead to restoration of the normal tissue, rather to the formation of tissue of lower grade, which in its earliest stages is known as **granulation tissue,** in its mature form as **cicatricial tissue**, the whole process being included under the title of productive inflammation.

The **phenomena of proliferation** begin in inflamed tissues, at the earliest after eight hours, but are first clearly recognizable after from twenty-four to forty-eight hours.

In general, they appear more rapidly the milder the inflammation and the more quickly as exudation is overcome or diminished. Suppuration, necrosis, and gangrene hinder proliferation and retard repair, or at least confine the reparative processes to neighboring tissues.

Every tissue capable of proliferation furnishes formative cells for tissue of its own kind or for one closely related to it. On the other hand, *newly developed tissue-cells may become mixed with the exudate, degenerate, and die.* Thus not all cells developed through proliferation fulfil their function of producing new tissue.

The **removal of the exciting cause of inflammation** takes place differently in different cases, and depends on the nature of the cause. Many traumatisms and thermal influences act for a short time, and have no further influence on the course of the inflammation. Substances acting chemically may be taken up by the tissue-juices and made inert, or excreted, while others remain locally active for a long time. *Insoluble bodies in the form of dust* which have penetrated into the tissue, for example, into the lungs, are for the greater part taken up by *phagocytes* and carried away (see § 21) and either deposited or removed from the body. Of the bacteria exciting inflammation, many die as the result of *bactericidal substances* formed in the diseased area (see § 31). *The destruction of bacteria takes place partly in the tissue-fluids* and partly by *phagocytosis,* the bacteria being taken up by the cells alive, or, having first been killed, are then digested. Of the bacteria causing inflammation, many live and produce new generations which in turn cause new inflammation, often in such a way that in the first focus the inflammation may subside and healing take place, while in the neighborhood, or even in distant regions, *metastatic inflammations* develop.

On account of the differences in the nature and behavior of the exciting cause of inflammation, as well as in the course of tissue-degen-

eration, exudation, and healing, it is easy to understand that the whole
course may vary greatly in different cases, and that all the possibilities
cannot be reviewed. At the same time it is not difficult to comprehend
the decline of the different forms of inflammation, since the whole proc-
ess is always made up of the same factors — that is, tissue-degeneration,
exudation, and proliferative processes, the last of which are intended to
counterbalance the disturbances caused by the first two.

The phenomenon of **chemotaxis,** that is, the attraction or repulsion of motile
cells by chemical substances soluble in water, was first observed by *Strahl* and
Pfeffer, who carried out observations on the myxomycetes, infusoria, bacteria,
spermatozoa, and zoospores. Investigations by *Leber, Massart, Bordet, Borissow,
Gabritschewsky,* and others have shown that the leucocytes likewise are attracted
by chemical substances (*positive chemotaxis*) or are repelled by them (*negative
chemotaxis*). In particular do products of fission-fungi (*Leber, Massart, Bordet,
Gabritschewsky*), or bacterial proteins, even in great dilution (according to *Buchner,*
pyocyaneus protein acts even in a three-hundred-fold dilution), possess positive
chemotactic action. According to *Buchner,* this property is also shown by gluten-
casein from wheat-gluten and legumin, aleuronate, glue from bones, and alkali
albuminates from peas, while ammonium butyrate, trimethylamin, ammonia, leucin,
tyrosin, urea, and skatol show negative chemotaxis.

III. Inflammatory New-formation of Tissue; Healing of Wounds and Substitution of Exudates and Tissue-necroses by Connective Tissue.

§ 95. The **inflammatory proliferation of tissue** is essentially a re-
generative process. Not rarely hyperplastic proliferations of con-
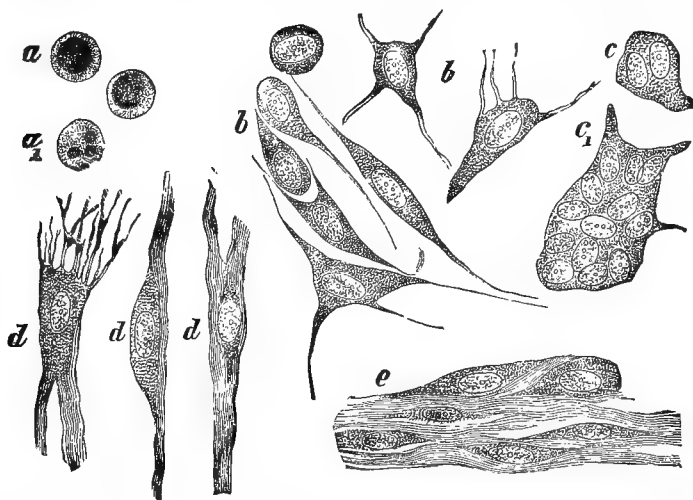
FIG. 187.—Isolated cells from a wound-granulation (Müller's fluid, picrocarmine). *a,* Mono-
nuclear, a_1, polynuclear leucocytes; *b,* different forms of mononuclear fibroblasts; *c,* fibroblast
with two nuclei; c_1, multinuclear fibroblast; *d,* fibroblasts in the stage of connective-tissue forma-
tion; *e,* fully developed connective tissue. × 500.

nective tissue fail to accomplish this purpose and cause new injury;
this is especially the case when persistent infection or the residues of
acute inflammation (exudates, abscesses, necroses) keep up a chronic
condition of inflammation.

The inflammatory new-formations of tissue may be distinguished from simple regeneration by the fact that they are accompanied by *circulatory disturbances* and *pathological exudations*, especially by *immigration of lymphocytes and leucocytes,* and that these have a modifying action on the course of the process.

The granulation tissue formed during inflammation is an **embryonic tissue arising through cell proliferation and infiltrated with**
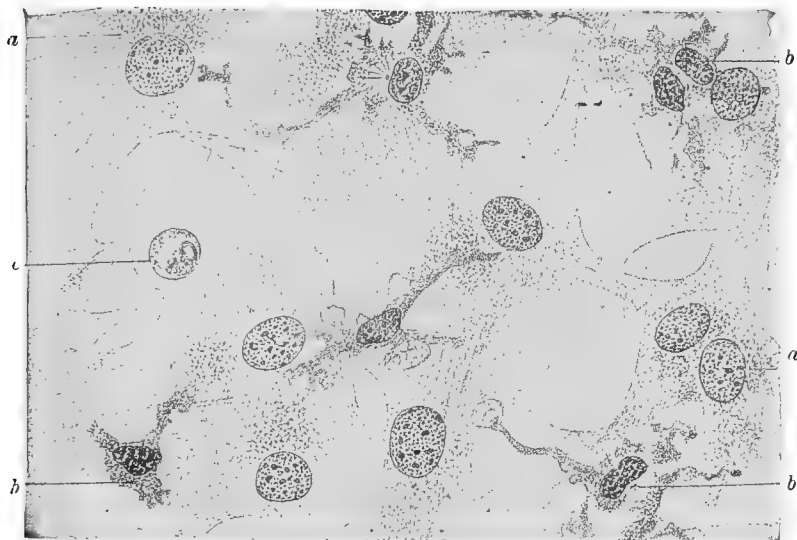
FIG. 188.—Scar fifteen days old (Maximow, l. c.). *a*, Fibroblasts; *b*, polymorphous lympho-cytes (polyblasts); *c*, unchanged lymphocyte (polyblast). × 500.

leucocytes and lymphocytes. In the beginning it consists essentially of *cells and of new-formed blood-vessels* which at first find support in the ground substance of the tissue from which they pass out, but soon form a *ground substance for themselves.*

The cells of granulation tissue are **proliferated tissue-cells** (Fig. 187, *b, c, d*), **polynuclear leucocytes** (a_1) and **mononuclear lymphocytes** (*a*). In most cases the proliferated cells are derivatives of fibrous connective tissue, and are known as **fibroblasts.** Granulation tissue, however, may contain derivatives of other tissues, for example, of periosteum, marrow-tissue, and muscle, in the form of *osteoblasts, chondroblasts,* and *sarcoblasts,* which are able to form bone, cartilage, and muscle, respectively. Further, newly formed *epithelium* may occur in glands, while in mucous membranes and in the skin new-formed *surface epithelium* may be found in or on the granulation tissue. The **fibroblasts of granulation tissue** are large polymorphous cells, with clear nuclei (Fig. 187, *b*), and may possess long processes. Young forms without processes resemble epithelial cells and are therefore called epithelioid cells. With the help of their processes they can push into the tissue spaces, but usually show no lively amœboid movements.

In the development of granulation tissue the **fibroblasts form connective-tissue fibrillæ,** a portion of the protoplasm taking on a fibrillar appearance, or first becoming homogeneous and then producing fibrillæ (Figs. 187, *d, e;* 188, *a;* 189, *a*).

The **polynuclear leucocytes** of granulation tissue (Fig. 187, *a*) are not capable of further development and either wander farther or die, particularly those which collect on the surface or in abscesses. If bacteria are present (streptococci, staphylococci, gonococci, anthrax-bacilli, etc.) the leucocytes may act as *phagocytes* (*microphages*) and aid in the destruction of the bacteria.

The **lymphocytes** and **mononuclear leucocytes** of granulation tissue arise from the blood, or are attracted from the lymphoid depots
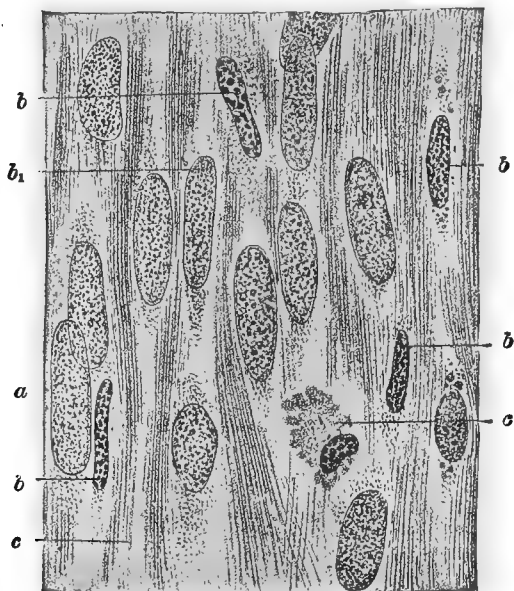
FIG. 189.—Tissue from a scar sixty-five days old (Maximow, l. c.). *a*, Fibroblasts; *b, b₁*, spindle-formed lymphocytes (polyblasts), with elongated nuclei embedded in the tissue; *c*, plasma cell. × 500.

and mingle with the cells of the exudate. Many of them die, as do the polynuclear leucocytes; or, on the other hand, may change into various cell-forms; from this they may be designated **polyblasts.** Enlargement of the protoplasm and enlargement and clearing of the nucleus give them the character of *epithelioid cells;* usually they are smaller than fibroblasts and their nuclei stain darker (iron-hæmatoxylin or methylene blue). *By sending out pseudopodia* they may assume *various forms* (Fig. 188, *b*). On the surface of smooth foreign bodies they may form an epithelial-like deposit or covering.

In the development of cicatricial tissue polyblasts, it is held, may be embedded as *permanent elements* in the form of *spindle cells* which are to be distinguished with difficulty or not at all from ordinary connective-tissue cells (Fig. 189, *b, b₁*). Occasionally they assume a character corresponding to that of the so-called *klasmatocytes* of Ranvier (Fig. 190, *b*), that is, they form spindle or branched cells, coarsely granular, showing many vacuoles and often containing granules staining metachromatically (polychrome methylene blue). Further, among the polyblasts of granulation tissue may be included the so-called *plasma-cells* (Figs.

189, *c*; 190, *c*), that is, round or irregularly formed cells having an eccentric nucleus and a bright central and dark granular periphery.

The *polyblasts* are those cells which show the greatest activity in granulation tissue as **phagocytes,** and not only take up bacteria but disintegrat-
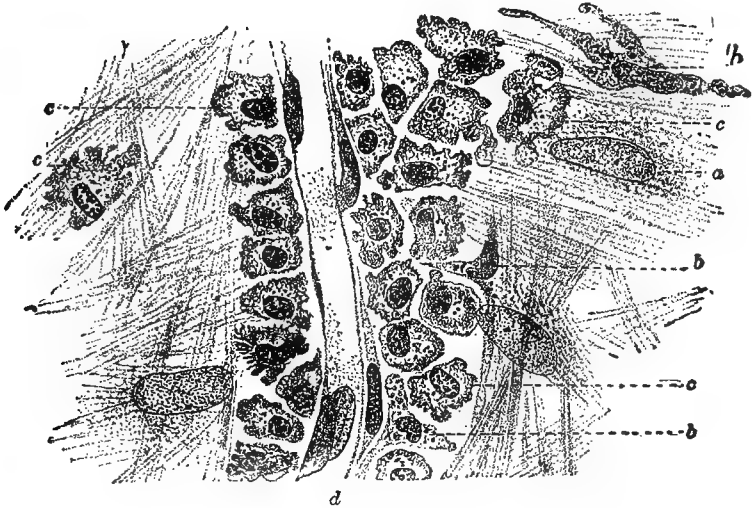
Fig. 190.—Plasma cells and klasmatocytes within scar tissue, forty days old (Maximow, l. c.). *a,* Fibroblasts; *b,* klasmatocytes; *c,* plasma cells; *d,* blood-vessel. × 500.

ing or dead red cells and leucocytes (Fig. 186), and destroy or carry them away.

They also have an inclination to form **multinucleated giant-cells** by continuous division of the nuclei in the same cell, usually by amitosis, rarely by karyokinesis, and *syncytial* forms, the latter, through *confluence of cells lying in close contact.* This is frequently observed
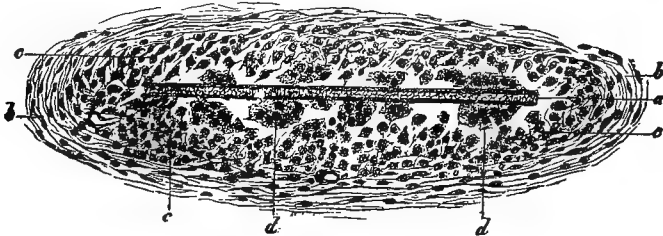
Fig. 191.—Dog's hair encapsulated in the subcutaneous tissue (alcohol, Bismarck brown), *a,* Hair; *b,* fibrous tissue; *c,* proliferating granulation tissue; *d,* giant-cells. × 66.

when foreign bodies or necrotic portions of tissue lie in the granulation tissue (Fig. 191, *d*); such multinucleated cells are therefore designated **foreign-body giant-cells.** Soluble substances, for example, catgut sutures or necrotic muscle-substance, can be gradually dissolved by them.

The presence of foreign substances in the form of the bodies of bacteria (tubercle-bacilli and lepra-bacilli) can also lead to their formation.

The **blood-vessels of granulation tissue** arise through offshoots from old vessels (see Fig. 140), which show proliferative processes early in the inflammatory state, (*a*), and in the formation of granulation tissue take on very lively proliferation. The young granulation tissue, as a result, becomes permeated by blood-vessels, so that it acquires a red appearance. During the transformation of granulation into connective or **scar-tissue, obliteration** of vessels occurs and the scar becomes pale.

The structure of granulation tissue, the origin and the fate of the cells contained in it, have been for decades the object of investigation and discussion, and even to-day not all of the questions can be regarded as solved. It has been demonstrated beyond doubt, however, that *the builders of cicatricial tissue,* the *fibroblasts,* are *derivatives of fixed connective-tissue cells;* further, it is certain that the *polynuclear leucocytes* emigrate from the blood and undergo no further development. The origin of the *small mononuclear cells* which resemble lymphocytes and the mononuclear leucocytes of the blood is still a matter of dispute, as is also the rôle which they play in the granulation-tissue.
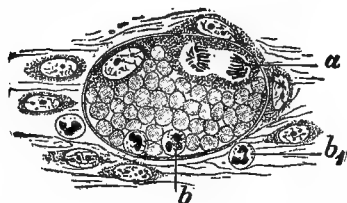
FIG. 192.—Cross-section of blood-vessel from the deep layers of the skin, forty hours after painting the skin of a rabbit with tincture of iodine (Flemming's solution, safranin). *a,* Endothelial cells with mitoses; *b, b₁,* leucocytes. × 350.

Even in the year 1876, on the ground of experimental investigations, I expressed the opinion that they were *capable of development into epithelioid cells* and that at the time of their formation and transformation they exert *phagocytosis* and take up other cells and digest them and that they can become changed into *permanent elements* of cicatricial tissue. I have demonstrated that under special conditions they form *syncytial giant-cells.*

Maximow, through investigations carried on in my laboratory in 1901-1902, has confirmed the view that the mononuclear leucocytes and lymphocytes, after passing out from the blood-vessels, may undergo further development, and has demonstrated that in cicatricial tissue they take on the appearance of *klasmatocytes, plasma-cells,* and *mast-cells,* also appearances similar to those of *ordinary fixed connective-tissue cells,* so that finally differentiation of the two original cell-forms is no longer possible. They also change to fixed connective-tissue cells, but do not produce, as I formerly assumed, the fibrillary ground-substance.

With reference to the varied forms which these cells show, *Maximow* has designated them polyblasts.

The differentiation of the different cell-forms as given above, rests essentially on differences in the structure of the protoplasm. **Plasma cells** (Unna) or the "krümelzellen" (*von Marschalko*) are mononuclear, round or oval, at times elongated cells that stain intensely with methylene blue and possess an eccentrically placed nucleus showing a chromatin network and five to eight chromatin granules. At the periphery of the cell the protophasm is more densely clumped, so that there is formed a lighter area surrounding the nucleus. The *klasmatocytes (Ranvier)* are spindle shaped, branched or stellate cells with blunt or swollen ends and a granular protoplasm that often contains little vacuoles. The *mast-cells (Ehrlich)* are round or flat or spindle-shaped cells, with numerous distinct coarse granules that, with the basic aniline stains, show an intense metachromatic reaction.

Cells of the character of lymphocytes, plasma-cells, and mast-cells occur in normal tissue and are regarded by some as tissue cells and by others as cells arising from the blood. The correct view is probably that which regards them as different stages of development of a mesenchymal group of cells to be separated from the tissue-building fixed cells, and to this group there should be added the polynuclear leucocytes and eosinophile cells. Certain stages of development are present in the blood, others are found in the tissue, partly in special tissue-formations (lymphadenoid tissue, bone-marrow), and partly in ordinary connective tissue. Under certain conditions it is possible that individual forms may pass into one another, for example, that lymphocytes may become transformed into plasma cells and klasmatocytes into mast cells.

§ 96. If on any part of the body there occurs an **open wound,** which does not become infected or otherwise seriously injured, the edges and base of the wound after twenty-four hours become deep red and somewhat swollen, and here and there small shreds of necrotic tissue may be seen. On the second day the gelatinous condition of the tissues is more apparent, the outlines of individual tissue-elements are effaced, and the color of the wound becomes grayish-red. From the second day on there appear over the wound small red papules, which increase in number and size, become confluent, and after two to three days form a granular surface. This is covered with more or less abundant secretion, which forms a gray, gelatinous layer, later becoming yellow and creamy. This layer consists of *coagulable exudate* and polynuclear leucocytes.

The changes which the surface of the wound show in the first two days are dependent on local hyperæmia, and the infiltration of cellular and fluid exudate, and on swelling and liquefaction of the tissue; as early as the second day there is proliferation leading to the development of **wound-granulations,** or *granulation tissue* (Fig. 193, *a*), *consisting of fibroblasts and leucocytes, and wide vessels* (*c*), among all of which there soon appears a *fibrillar ground-substance*. The leucocytes, which are mostly of the polynuclear form, are found in all the layers in fresh granulations, but heap themselves particularly in the superficial strata, and, *embedded in fibrin*, cover the surface (*b*). The fibroblasts are found most abundantly in the deeper layers (Fig. 193, *a*), and it is here that the new-formation of connective tissue proceeds most actively.
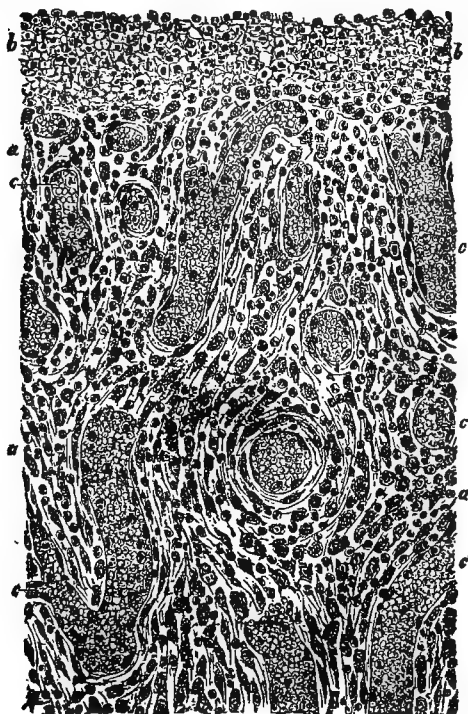
Fig. 193.—Wound-granulations from an open wound with fibrinopurulent covering (Müller's fluid, hæmatoxylin). *a*, Granulation tissue; *b*, fibrinopurulent layer; *c*, blood-vessels. × 135.

When a certain degree of fibrillæ-formation has been reached, the process comes to a standstill, the fibroblasts with their nuclei remain as fixed connective-tissue cells (Fig. 187, *e*), and attach themselves to the surface of the fibrillæ. The process has now reached its termination — *granulation tissue has become* **scar-tissue.**

In **open wounds of the skin,** when infection does not disturb the course of healing, the formation of granulation tissue lasts until the wound is covered with epithelium. The regeneration of the latter proceeds from the edges, the epithelium gradually pushing itself over the

granulations. With the formation of connective tissue the reproductive processes terminate, but transformation processes continue in the cicatricial tissue for some length of time. Shortly after its formation the cicatrix is rich in blood and appears red; later it loses a portion of its vessels through obliteration, becomes pale, and contracts to much less than the original volume. Large scars of the skin show permanently a smooth surface, since the papillary bodies are not again formed or only imperfectly (Fig. 195, e). The scar remains for several months abnor-
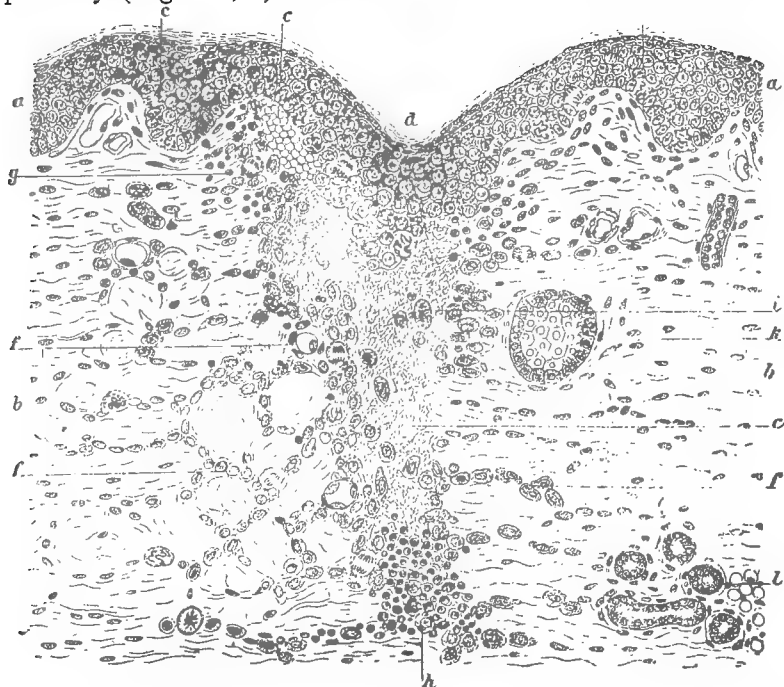
Fig. 194.—Healing of incised wound of skin united by suture (Flemming's solution, safranin). Preparation made on the sixth day. a, Epidermis; b, corium; c, fibrinous exudate, in part hæmorrhagic; d, newly formed epidermis, containing numerous division-figures, and with plugs of epithelium extending into the underlying exudate; e, division-figures in epithelium at a distance from the cut; f, proliferating embryonic tissue, developing from the connective-tissue spaces, and containing cells with nuclear division-figures, and in part also vessels with proliferating walls; g, proliferating embryonic tissue with leucocytes; h, focus of leucocytes in deepest angle of wound; i, fibroblasts lying within the exudate, one showing a nuclear division-figure; k, sebaceous-gland; l, sweat-gland. × 70.

mally rich in cells, but in time becomes poor in cells and firm in consistence.

When the healing of a wound occurs in such manner that the defect is closed by granulation tissue visible to the naked eye, the process is designated *repair by second intention (per secundam intentionem)*.

Incised wounds of the skin, *whose edges are united by sutures, grow together by first intention,* and healing takes place in essentially the same manner as that of an open wound by second intention; but inflammation, proliferation, and new-formation of tissue are less prominent, partly because they take place below the skin, and partly because they are of less extent and intensity.

The result of such a cut is hæmorrhage together with more or less abundant exudation (Fig. 194, c), which glues the opposing wound-sur-

faces. Soon there arises inflammatory infiltration of the edges of the wound, which varies greatly in different cases, and when repair is aseptic never reaches a significant degree (*g, h*), attaining its maximum in from two to four days, diminishing from the fifth to the seventh day, and completely disappearing at or soon after the end of the second week. The inflammatory infiltration is usually greater in the neighborhood of the sutures than at the edges of the wound.

As early as the second day regenerative processes begin in the con-
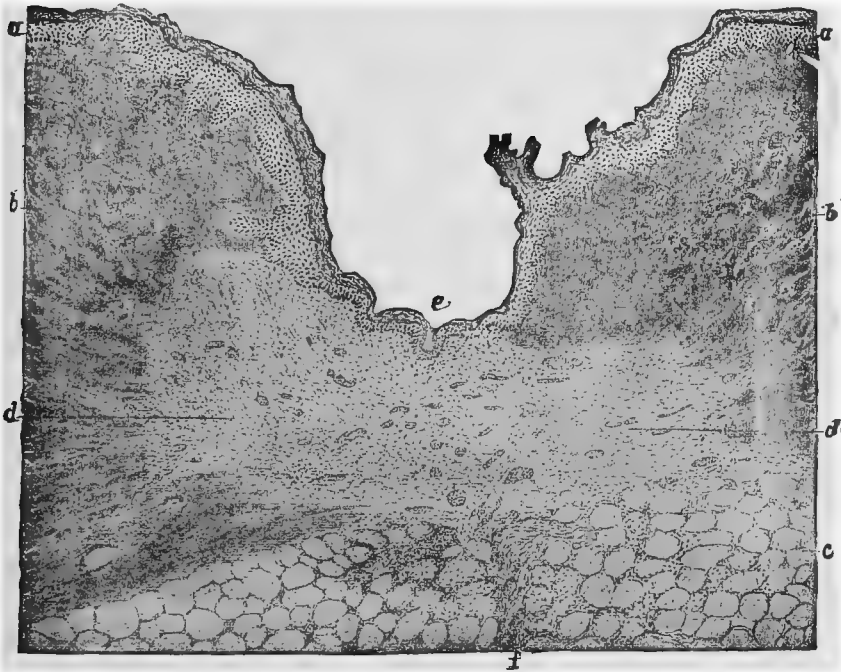
FIG. 195.—Cutaneous portion of a laparotomy cicatrix, sixteen days after the operation (Müller's fluid, hæmatoxylin, Van Gieson's). *a*, Epithelium; *b*, corium; *c*, subcutaneous fat tissue; *d*, scar in corium; *e*, new epithelial covering; *f*, scar in fat tissue. × 38.

nective tissue and in the vessels, and lead, in the course of several days, to the formation of embryonic tissue at the edges of the wound (Fig. 194, *f*), partly extending into the wound itself (*i*); and gradually replacing the coagulum. This tissue is present in varying quantity in different parts of the wound (Fig. 194). After a time, varying according to the size of the wound, the thickness of the exudate, and the intensity of proliferation, the masses of embryonic tissue growing from the edges of the wound blend and young connective tissue joins the edges together, and at the same time extends into the old tissue, so that the boundary between old and new becomes indistinct.

While connective tissue is being formed in the deeper parts of the wound, the epithelium on the surface is also being regenerated (Fig. 194), and through continuous cell-divisions (*d, e*) forms a covering of many layers.

The young connective tissue uniting the edges of the wound is distinguishable for a long time from the neighboring older tissue through its

richness in cells (Fig. 195, *d*, *f*), and the finer fibrillation of its ground-substance; in large incised wounds of the skin there may be found in the scar, after the lapse of weeks or even months, slight evidence of proliferation and inflammation. In general, however, transformation processes gradually occur in the scar, so that its t i s s u e s approach more closely to the normal, and finally the place of incision can no longer be easily recognized. If the wound heals by the interposition of abundant embryonic tissue, there may occur a defect of the papillary b o d i e s (Fig. 195, *e*), so that the scar remains smooth.

§ 97. When on the surface of an **inflamed serous membrane** (Fig. 196, *a*) there is an **adherent layer of fibrin** (*b*), beneath it **granulation tissue** is apt to form rapidly.
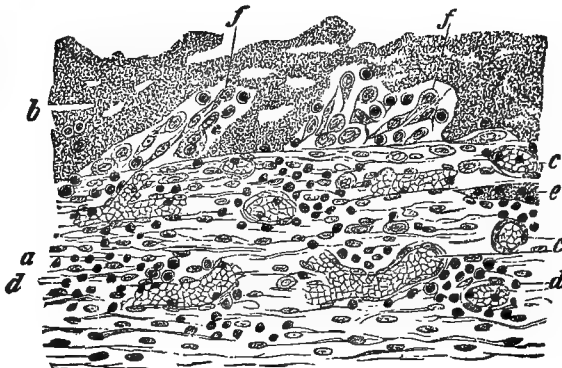
FIG. 196.—Fibrin deposit and beginning formation of granulation tissue in a fibrinous pericarditis five days old (Müller's fluid, hæmatoxylin). *a*, Epicardium; *b*, fibrin-membrane; *c*, dilated, congested vessels; *d*, round cells infiltrating the tissue; *e*, lymph-vessel filled with cells and clots; *f*, fibroblasts within the deposit. × 150.
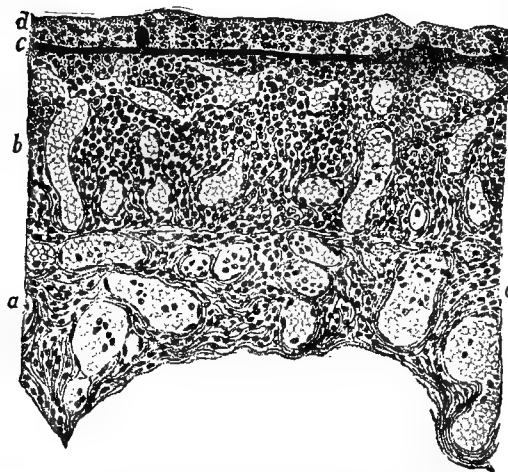
FIG. 197.—Development of granulation tissue in the pleura, in bronchopneumonia and pleuritis of fourteen days' duration (alcohol, Van Gieson). *a*, Hyperæmic, infiltrated pleura; *b*, very vascular granulation tissue; *c*, fibrin; *d*, pus-corpuscles, and granules of precipitated albumin. × 100.

The beginnings can be seen as soon as the fourth day and consist in the appearance of *fibroblasts* (*f*) in the deepest layers of fibrinous membrane. These arise through proliferation of the connective-tissue cells of the affected part, and penetrate the fibrin. There follows s o o n new-formation of blood-vessels, and in the course of days or of weeks there is developed on the surface vascular embryonic or granulation t i s s u e, which, when the overlying fibrin is compact, lifts this up *in toto* (Fig. 197, *b*, *c*); or penetrates the interstices o f t h e fibrin-membrane (Figs. 196, *f*; 198, *b*, *d*), and in time replaces the fibrin. Remains of fibrin (Fig. 198, *c*) may, however, persist for weeks or months in the granulation tissue.

In the formation of granulation tissue and the development of scar-tissue the epithelium (endothelium) of the serous membranes takes
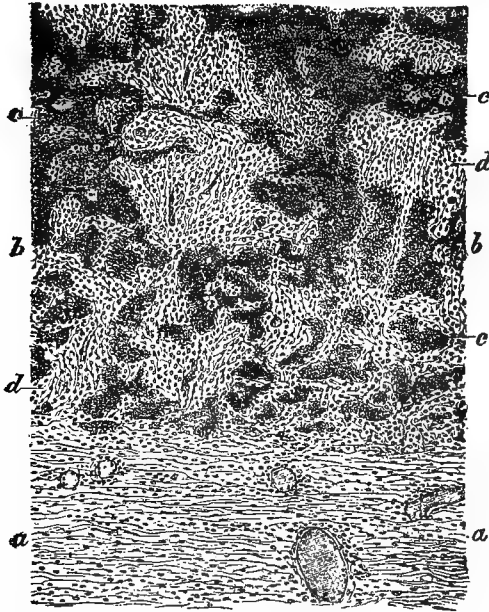
Fig. 198.—Formation of granulation tissue in the fibrinous deposits of a pericarditis several weeks old (Müller's fluid, hæmatoxylin, eosin). *a*, Epicardium; *b*, deposit on the epicardium, consisting of granulation tissue (*d*), and fibrin (*c*). × 40.

no part, since it produces no fibroblasts. On the other hand, the products of the inflammatory proliferation become covered later with epithelium.

The result is the formation of **connective tissue,** which leads either to *thickening* of the serosa or to *adhesion of opposing surfaces,* so that the inflammation may be designated *adhesive.* The result in individual cases depends on the amount of fibrin and the situation of the affected organ, and its condition during the process of healing.

Small deposits of fibrin, limited to one surface of the serous membrane, lead to thickenings of the serosa, which, becoming pale with the obliteration of vessels, are finally represented by so-called milk-spots or **tendinous spots.** The glueing together of two serous layers by abundant fibrin leads to an **adhesion** through the formation of connective tissue. In the case of a smaller amount of fibrin, and repeated rubbing of the membranes upon each other, there develop loose *membranous* or *stringy adhesions,* which still permit the serous surfaces to move upon one another. Very large amounts of *fibrin* may permanently resist absorption and usually become *calcified.*

Coagulated exudates in the lungs may become liquefied and *absorbed,* but it sometimes happens that their removal is associated with connective-tissue proliferation and *induration of the lung.* The proliferation proceeding from the lung tissue leads to thickening of the septa (Fig. 199, *a, b*) or extends into the exudate in the alveoli in

Fig. 199.—Intraseptal and intra-alveolar formation of connective tissue in the lung (alcohol, hæmatoxylin). *a*, Thickened fibrocellular alveolar septum, in part infiltrated with round cells (*b*); *c*, fibrinocellular exudate in the alveoli; *d*, intra-alveolar formative cells: *e*, strand of spindle-cell fibroblasts; *g*, intra-alveolar newly formed blood-vessel. × 200.

18

the form of embry-
onic tissue (*d, e*)
which later may con-
tain newly formed
blood-vessels (*g*).

**Masses of coagula
within blood-vessels,**
called thrombi, give
rise, in case no in-
fection occurs, to in-
flammatory prolifera-
tion of the vessel-
wall, a *proliferating
vasculitis.* This pro-
cess corresponds ex-
actly to the inflam-
matory proliferation
of serous membranes.
It is i m m a t e r i a l
whether   thrombosis
has been caused by a
preceding inflamma-
tory process or by
other conditions, inas-
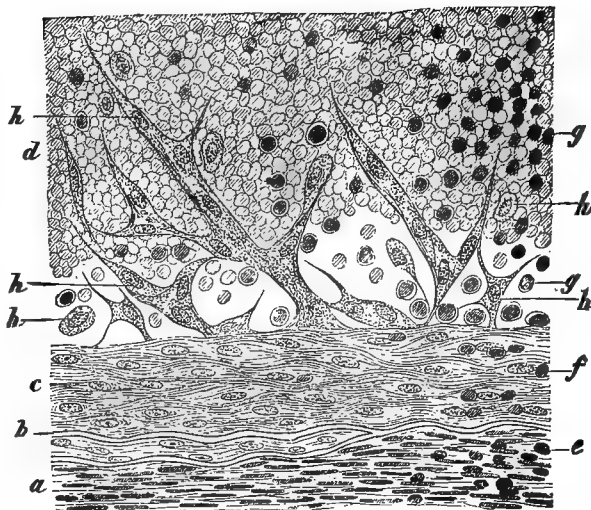
FIG. 200.—Development of embryonic tissue in a thrombosed femoral artery of an old man, three weeks after ligation (alcohol, hæmatoxylin). *a*, Media; *b*, elastic limiting membrane; *c*, intima, thickened through older inflammatory processes; *d*, coagulated blood; *e*, cellular infiltration of the media, *f*, of the intima; *g*, round cells, partly in the thrombus, partly between it and the intima; *h*, different forms of fibroblasts. × 300.

much as the mere presence of the coagulum is sufficient to cause inflam-
mation and tissue-proliferation.
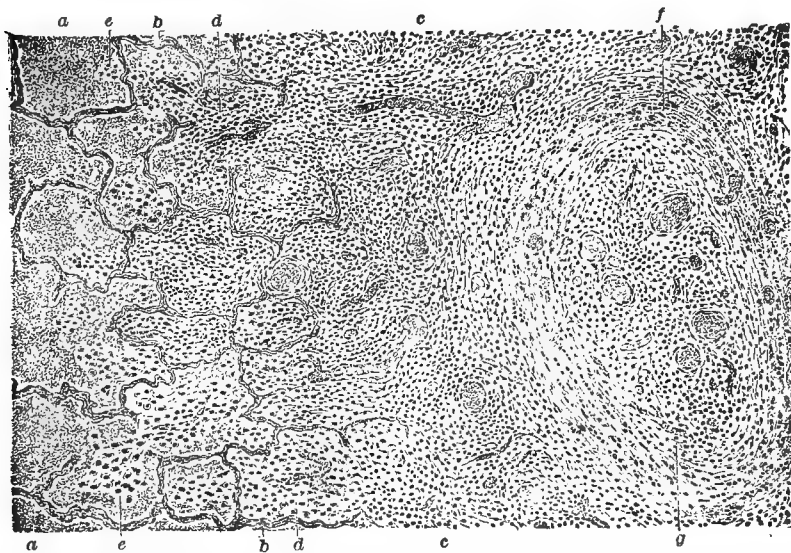
FIG. 201.—Periphery of a healing pulmonary infarct (Müller's fluid, hæmatoxylin, eosin). *e*, Blood-extravasate changed into a yellowish granular mass; *b*, necrotic alveolar septa without nuclei; *c*, newly formed connective tissue; *d*, vascular granulation tissue within the alveoli; *e*, fibroblasts within alveoli containing the residue of the hæmorrhage; *f*, artery; *g*, vascular con-
nective tissue formed within the artery at the place of the embolus. × 40.

The first change introduced in the **substitution of the thrombus by connective tissue** is the appearance of *fibroblasts* (Fig. 200, *h*), which arise from the vessel-wall, and later, with the aid of vessels growing in from the vessel-wall and its neighborhood, form embryonic tissue, which ultimately changes into connective tissue. The complete substitution of an obturating thrombus leads to obliteration of the vessel-lumen by vascularized connective tissue (Fig. 201, *g*); the substitution of a parietal thrombus, on the other hand, results in the formation of fibrous thickening of the vessel-wall. As the result of imperfect substitution or liquefaction of the part not substituted, strands and threads of connective tissue cross the lumen of the vessel. Calcification of portions of thrombi not replaced by connective tissue leads to the formation of vessel-stones (arterio- or phleboliths).

FIG. 202.—Fibroid area in heart-muscle. Section through a muscle-trabecula which has undergone fibroid change (Müller's fluid, hæmatoxylin). *a*, Endocardium; *b*, cross-section of normal muscle-cells; *c*, hyperplastic connective tissue rich in cells; *d*, atrophic muscle-cells in hyperplastic connective tissue; *e*, dense connective tissue, poor in nuclei and containing no muscle-cells; *f*, vein, in whose neighborhood muscle-cells are still preserved; *g*, small blood-vessels; *h*, small-cell infiltration. × 40.

Necrotic tissue which cannot be sequestrated and discharged externally, is also **replaced by vascular connective tissue**, which becomes converted into **scar-tissue**; this substitution takes place in the same manner as in fibrinous exudates and thrombi. The requisite condition is that the necrotic tissue shall contain no substances (bacteria) which hinder tissue-proliferation. In general it is immaterial how the necrosis has occurred, or whether the necrotic tissue is free from or infiltrated with exudate or blood. The change leading to healing consists in the production of **granulation tissue**, which grows toward the necrotic tissue (Fig. 201, *c*, *d*), and finally replaces it. If this process is not disturbed large tissue-necroses (for example, a hæmorrhagic infarct of the lung) may in the course of weeks or months disappear and be replaced by connective tissue. It may also happen, however, that certain tissues resist absorption, or that the development of granulation tissue stops so early that remains of *the necrosed tissues persist and become calcified*.

When, as the result of inflammation or ischæmia, only the more sensitive elements die — for example, epithelial or muscle cells — while the connective tissue remains intact, the absorption of necrotic portions takes

place quickly, and there is formed in a short time a *scar of connective tissue* (Fig. 202, *e*), in which specific tissue-elements are lacking.

Pus is quickly *absorbed* from small abscesses, and the *defect is closed by granulation and scar tissue.* Large amounts of pus may be absorbed from the body-cavities and from the lungs.

Abscesses cause in their immediate neighborhood **granulation tissue** which leads to the formation of a limiting, so-called pyogenic or **abscess-membrane.** The abscess-cavity may become obliterated through absorp-

tion of the pus and union of the walls of the cavity; the abscess finally heals and leaves a **scar.** Incomplete absorption may lead to thickening of the pus and *calcification* of the *residue.* If the pus does not become inspissated, the **abscess may persist** and increase in size by exudation from its walls.

Empyemata may heal in similar manner to abscesses through the absorption of pus. The tissues enclosing the pus produce **granulation-** and **scar-tissue,** which may reach a considerable size when absorption is delayed (Fig. 204). When incompletely absorbed, *calcification may occur.*

Foreign bodies, so far as they are absorbable and exert no specific influence on their surroundings, are dissolved, and replaced by connective tissue in the same way as are tissue-necroses or fibrin masses. If they possess accessible interstices, these may be penetrated by granulation tissue. If not absorbed, they become encapsulated.
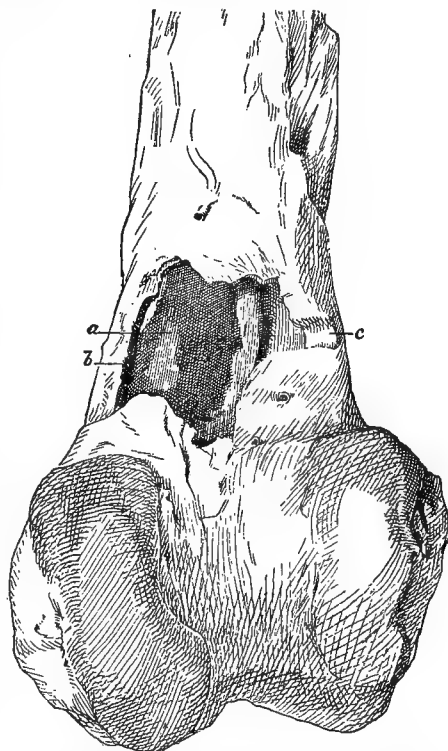
Fig. 203.—Necrosis of fifteen years' duration in the lower part of the diaphysis of the femur. *a*, Sequestrum; *b*, *c*, edges of the opening in the thickened bone (alcoholic preparation). Reduced one-third.

IV. Chronic Inflammations.

§ 98. Inflammation is essentially an acute process, but various conditions may cause the phenomena of tissue-degeneration and exudation to persist, and inflammation then becomes chronic.

The **causes of chronic inflammations** are to be sought in the fact that *in an acute inflammation changes occur which prevent healing.* When masses of necrotic tissue are not completely absorbable, such as large pieces of bone, they may become sequestrated, but persist as sequestra for years (Fig. 203, *a*), and keep up inflammation. Following a large, superficial defect of the skin, such as results from a burn, granulation tissue

develops, but months may pass before the wound is covered with epithelium from the edges and the process brought to a close.

A further cause of chronic inflammation is *constantly repeated injury.* For example, frequently repeated inhalation of dust may cause chronic inflammation of the lungs; repeated rubbing of the skin may cause chronic inflammation of the part affected; pathological alterations of the stomach contents may cause chronic inflammation of the stomach. In canals or reservoirs, such as the gall-bladder, the ducts of the pancreas, etc., *concretions* may give rise to lasting tissue-lesions.

Unfavorable nutritive conditions — e. g., marked congestion — may enable external influences that, under normal conditions, produce no inflammation at all or one soon subsiding, to set up ulcerative processes showing no tendency to heal. In this manner, for example, chronic ulcers of the leg may arise.

A frequent cause of chronic inflammation is furnished by *infections,* particularly . *bacteria* and *moulds,* which multiply in the body and constantly give rise to irritation. The inflammations which they cause are distinguished by the fact that they lead to connective-tissue proliferations and that they usually show a *progressive character,* and form secondary deposits through the lymph- and blood-vessels.

Finally, *chronic intoxications* form a cause. These
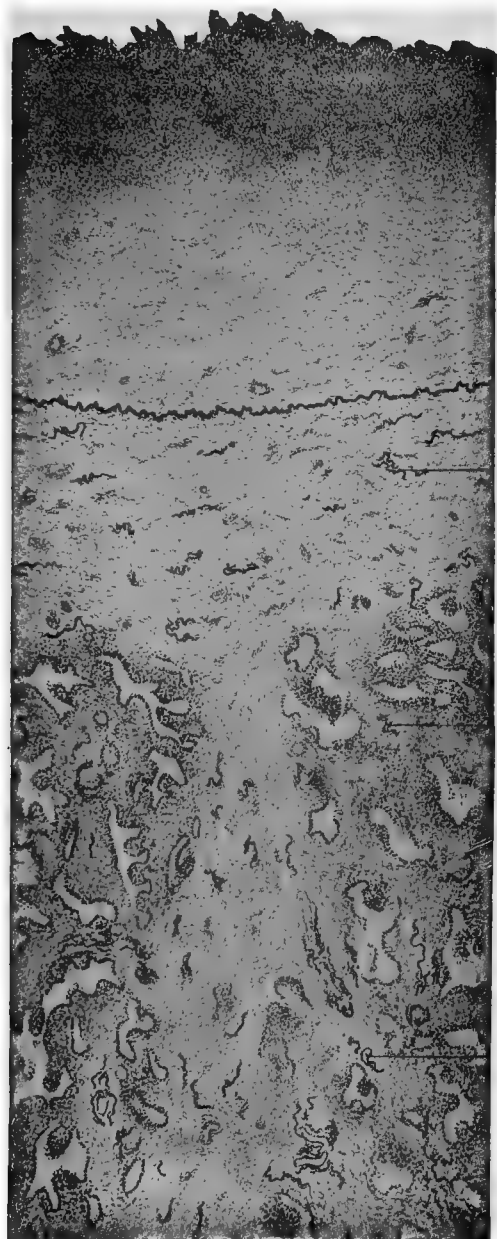
FIG. 204.—Changes in the pleura and lung after a purulent pleuritis lasting six months (alcohol, orcein). *a,* Thickened lung tissue with gland-like alveoli, and elastic fibres in the newly formed connective tissue; *b,* thickened pleura; *c,* newly formed connective tissue without elastic fibres; *d,* granulation tissue covered with pus; *e,* elastic limiting membrane of the pleura; *f,* elastic fibres. × 46.

affect chiefly the kidneys and liver, and may be attributed either to the continued introduction through the gastro-intestinal tract, lungs, or skin of substances harmful to the organs directly concerned or to others; or injurious substances may be produced in the body itself, through disturbances of metabolism.

The **forms of chronic inflammation** are determined partly by their causes, partly by the character of the tissue affected.

FIG. 205.—Section of a stonecutter's lung with fibroid nodules (alcohol, picrocarmine). *a*, Group of fibroid nodules; *b*, normal lung tissue; *c*, thickened lung tissue still containing bronchi, vessels, and a few alveoli. × 9.

Chronic inflammations characterized by **hyperplastic formations of connective tissue** are found in serous membranes, lungs, and skin, but may occur in other tissues. Chronic pleuritis, caused by exudates which are with difficulty absorbable, or by chronic infections, lead to extensive *scar-like thickenings* (Fig. 204, *b, c*), on the pleura (*c*) and in it (*b*). Moreover, *induration of the lung* (*b*) may follow *infectious inflammations,* or may be caused by the continued *inhalation of stone dust,* the latter characterized by the formation of fibroid nodules (Fig. 205; *a*), or by diffuse induration (*c*) Continued irritation of the orifices of the urogenital apparatus, through the discharge of secretions (chronic gonorrhœa),

FIG. 206.—Condyloma acuminatum (injected preparation). *a*, Enlarged branching papillæ; *b*, epidermis. × 20.

frequently leads to the formation of *pointed condylomata* (*condylomata acuminata*), in which inflamed and infiltrated papillæ grow out with their vessels (Fig. 206, *a, b*) and divide into branches.

Frequently repeated or continued slight inflammations of the skin and subcutaneous tissue, due to mechanical lesions, parasites, or other irritation, may, if they reach a considerable extent, give rise to diffuse hyperplasia of connective tissue, known as *elephantiasis.*

Inflammatory proliferations of the periosteum and bone-marrow, which give rise to *pathological new-formations of bone or hyperostoses* (Fig. 207), may be caused both by non-specific irritations — for example, by inflammations which run their course in the neighborhood of chronic ulcers — as well as by specific infections — for example, syphilis or tuberculosis.

Chronic catarrhs of mucous membranes are caused by specific infection (gonorrhœa, tuberculosis), by non-specific injuries (concretions, pathological changes in the gastric or intestinal contents), and by continued disturbances of circulation (congestion).

Chronic abscesses usually arise from acute abscesses, and have the same etiology; but may develop gradually and are then caused by such infections as tuberculosis and actinomycosis. They are usually limited by

Fig. 207.—Periosteal hyper-ostosis of the tibia, at the base of a chronic ulcer of the leg. Reduced two-fifths.

a connective-tissue membrane lined on the inside by granulation tissue, and may increase in size through secretion of pus from the abscess-wall, and through destruction of the wall and neighboring tissue. Progressive extension toward the deep parts leads to the formation of **burrowing abscesses.** Their increase in size is always to be ascribed to persistence of infection. Perforation into neighboring tissues leads to secondary infective inflammations.

The tuberculous and actinomycotic forms of chronic abscesses are distinguished by the specific character of the pus and by the peculiar structure of the abscess-membrane (see Tuberculosis and Actinomycosis, Chapter X.).

Chronic ulcers are caused chiefly by specific infections (tuberculosis, syphilis, glanders), but non-specific agents may lead to chronic ulcerative processes in tissues which are especially susceptible. Thus chronic congestion in the vessels of the leg may have such an effect that ulcers arising through any influence may be prevented from healing under the mechanical conditions in which the leg finds itself. Likewise peculiar qualities of the stomach contents may hinder the healing of an ulcer of the stomach. If healing begins at one edge of an ulcer while ulceration advances at other parts, the ulcer is known as *serpiginous.* The excessive development of granulation tissue in an ulcer leads to the production of the condition known as exuberant granulation, or "proud flesh;" dense thickening of the edge and base gives rise to the form known as *indolent ulcer.*

Chronic proliferations of granulation tissue — i. e., *granulations which persist* without becoming changed into connective tissue — occur in various **specific infections,** notably in *tuberculosis, syphilis, leprosy, glanders, rhinoscleroma,* and *actinomycosis.* Since the granulations in these infections form fungoid proliferations and tumor-like formations, they are often called **fungous granulations** or **infectious granulomata.** All these show certain structural and other peculiarities which enable us to recognize their specific nature (see Chapter X.). It should be noted, however, that the etiology of some of the granulomata is still unknown.

Chronic inflammations in which **atrophy of specific tissue** is associated with **hyperplasia of connective tissue,** occur particularly often in the mucous membrane of the gastro-intestinal tract, and in the kidneys and liver.

In the **intestinal canal** the cause may lie in specific infections (dysentery) as well as in non-specific irritations; the latter dependent on some abnormal property of the contents of the canal. The epithelial elements may undergo necrosis with persistent desquamation, the connective tissue being unaffected; or they may necrose and disintegrate at the same time as the connective tissue on which they rest. The result is a mucous mem-
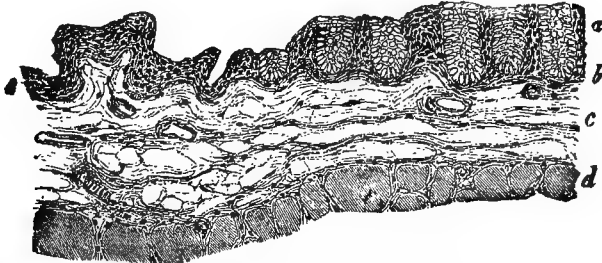
Fig. 208.—Section through the mucosa of an atrophic large intestine, (alcohol, alum-carmine). *a,* Glandular layer decreased to one half its normal height; *b,* muscularis mucosæ; *c,* submucosa; *d,* muscularis; *e,* total atrophy of the mucosa. × 30.

brane (Fig. 208) which either contain no glands (*e*) or only rudimentary ones (*a*).

In the **liver** and **kidneys** the chronic inflammations which lead to atrophy and induration, and whose results are respectively known as **cirrhosis of the liver** and **indurated** or **contracted kidney,** are hæmatogenous diseases, in so far as they do not depend on disturbances in the efferent passages (obstruction, inflammation of pelvis of kidney, formation of concretions), and are caused partly by *infections* and partly by *intoxications.* They may begin as acute inflammations or insidiously, and are characterized by atrophy and degeneration of glandular tissue, hyperplasia of connective tissue, cellular infiltration, formation of granulation tissue, obliteration of old vessels, and the formation of new vessels. In the liver new bile-ducts are often encountered, which, however, for the greater part do not functionate.

CHAPTER VIII.

Tumors.

I. General Considerations.

§ 99. A **neoplasm,** or **autonomous new-growth, atypical blastoma,** or **tumor** in the commonly accepted sense, is a *new-formation of tissue, apparently arising and growing independently, having an atypical structure, inserted uselessly into the organism, possessing no function of service to the body, and showing no typical termination to its growth.* The atypical character of a tumor is shown in its external appearance as well as in its internal organization in that it departs more or less in structure from that of a normal organ or tissue. When this departure is slight, the structure of the tumor approaches closely to that of the hypertrophies; in fact, there are cases in which the difference in structure is so slight that it becomes difficult to decide whether an excessive new-growth of tissue is to be classed as tumor or hypertrophy.

Tumors may develop in any tissue of the body which is capable of growth, and **arise through proliferation of tissue-cells,** associated with **new-formation of blood-vessels.** Not infrequently *leucocytes and lymphocytes* emigrate into the tumor, and exudative processes and inflammatory proliferations may take place in it or its neighborhood, *but these phenomena form no essential part of the development of the tumor.*

The processes of cell-division and of new-formation of blood-vessels are the same as those described in §§ 80 and 82 — i. e., division of cells takes place by karyomitosis, and new vessels are formed from buds given off by old vessels. The mitoses are for the greater part typical (Fig. 209, *b*), but there are also atypical forms, such as asymmetrical divisions, nuclear figures with abnormally large chromatin masses (so-called giant mitoses), pluripolar mitoses, nuclear fragmentation, and direct segmentation.

In their fully developed condition tumors are often well defined *from surrounding tissues,* but in some cases *may pass into the neighboring tissue without any sharply defined border of transition.* Further, *an entire organ may become transformed into a tumor, or large portions of tissue not sharply outlined from their surroundings may take on the character of a tumor.* Through the disintegration of tumor tissue ulcers frequently arise.

The difference between the structure of a tumor and that of normal tissue is usually recognizable macroscopically, but there are tumors which so closely resemble the tissue from which they arise that the difference can be made out only through more careful examination.

The *circumscribed tumors* are usually *nodular* (Figs. 210, *d;* 212; 213, *a*). The size of the individual nodules varies, according to the kind of tumor and the stage of development, from miliary and submiliary nodules to masses weighing ten to twenty kilograms or more. When situated on the surface of an organ nodular tumors not infrequently take on the form of a sponge (Fig. 210, *d*) or of a polyp, and are accordingly designated *fungoid* or *polypoid tumors.* When a new-growth on the surface of a

mucous membrane or the skin leads to enlargement and branching of the papillæ, or if new papillæ are formed, there arise *warty, verrucose,* and *papillary tumors* or *papillomata* (Fig. 211). Further development of the papillary structure may lead to *dendritic branching* and the formation of a *cauliflower mass.*

Tumors usually develop from small beginnings; rarely do they arise from centres extending diffusely through an organ. Growth may be rapid or slow, sometimes with periods of quiescence, or it may be suspended for years, and then suddenly become active.

The **structure of the tumor** *is determined by the tissue from which it takes its origin;* and although true tumors always show a certain *atypical character,* yet they retain certain characteristics of the parent tissue.

According to their structure and genesis tumors may be broadly
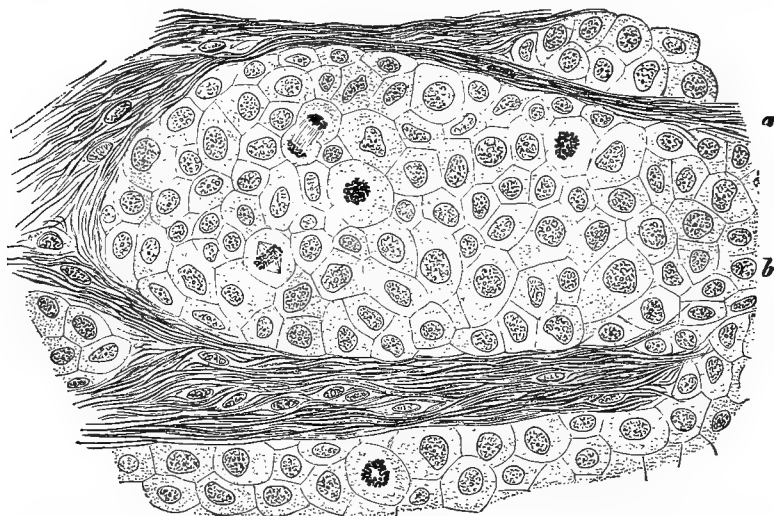
Fig 209.—Tissue from a carcinoma of the breast, containing numerous division-figures in different phases of mitosis (Flemming's solution, safranin). *a,* Stroma; *b,* epithelial plugs. × 500.

divided into three groups: 1, *connective-tissue tumors;* 2, *epithelial tumors;* 3, *teratoid tumors and cysts.* It should be noted, however, that there are many forms of tumors which, according to one's point of view, may be classed as belonging to two, or even to all three groups.

The **connective-tissue tumors** or **tumors arising from the supporting-tissues,** often called *histoid tumors,* consist of tissues which in structure correspond to mature or to embryonal connective tissue, and take their origin from mesodermal tissues. Ordinarily there are included in this group tumors arising from glia cells, and muscle-tumors, since these in structure resemble the connective-tissue tumors more than they do the epithelial.

The differences in type of connective-tissue tumors are dependent on the character of the ground-substance and cells. When such tumors are rich in cells and the ground-substance is only slightly developed, they acquire a soft consistence and are classed with the *sarcomata.* Through combination of different forms of connective tissue *mixed connective-tissue tumors arise.*

The **epithelial tumors** are composed of cells derived from surface or glandular epithelium, and vascularized connective tissue forms a framework in which the tumor cells lie in definite groups. Inasmuch as this arrangement gives to the tumors a structure suggesting that of a gland, they are often called *organoid tumors,* in contradistinction to the histoid or connective-tissue tumors. It should be noted, however, that there are also included in the connective-tissue group of tumors certain varieties (endotheliomata) which have an organoid structure.

The cells which give the epithelial tumors their special character arise from the ectoderm or entoderm, and from the glands developing from the same, or from the mesodermal epithelium of the pericardium, and of the pleural and peritoneal cavities, or of the glands arising from this layer (kidneys, sexual glands, adrenals). Tumors having the last-named origin often show more or less distinctly the character of the parent tissue.
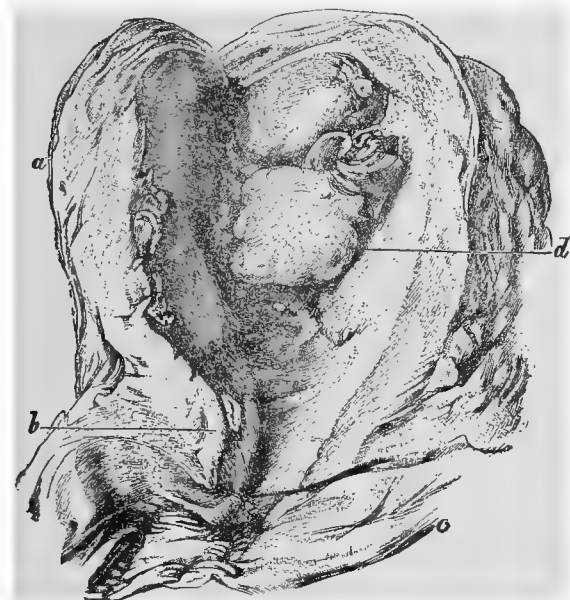
FIG. 210.—Fungoid carcinoma of the endometrium of the posterior wall of the uterus. *a,* Body of the uterus; *b,* cervix; *c,* vagina; *d,* tumor. Two-thirds natural size.

Very soft epithelial or connective tissue tumors are designated *medullary.*

Combinations of epithelial hyperplasia and proliferations of connective tissue which exceed the ordinary amount of supporting tissue or bear a sarcomatous character, lead to the formation of epithelial *mixed tumors.*

Teratoid tumors and teratoid cysts form a group which is characterized by the fact that they contain various sorts of tissue derived from all three germ-layers (*teratoid mixed tumors*), or by the presence of certain tissues in regions where they do not normally occur. Tumors, therefore,

FIG. 211.—Papillary adenoma of rectum. Natural size.

which according to their structure may be placed in one or the other groups, may be considered as teratomata on account of their situation. Further, there are included in the group of teratoid tumors certain formations which according to their structure, origin, and physiological relations ought not to be classed with the tumors.

Tumors usually develop **singly**; but it also happens that within a certain tissue system there may appear coincidently or in succession **a great number of tumors of the same kind,** so that it must be assumed that conditions requisite for their development were present in different parts of the same system at the same time. At times there develop in different organs of the *same* individual two *entirely different varieties of tumors,* which stand in no relation to each other, and whose coincident appearance is accidental.

The determination of what should be included under the term **tumor** is hardly possible; consequently the designation tumor is applied to many different formations which, according to their etiology, genesis, and life-characteristics, have not the same significance. The idea of tumor is, therefore, differently conceived by different authors. I regard it as advisable, as based on the life-characteristics of the tissue-formations which we are about to consider, to exclude from the class of tumors all hyperplastic proliferations, and cysts which arise through the retention of secretions, and which show no independent new-formation of tissue. Further, according to my view, *there should be separated from the true tumors all proliferations of tissue due to the presence of parasites or to infection,* particularly the granulomata of tuberculosis, syphilis, leprosy, etc. Should it be proved that some of the new-growths now included with the true tumors are caused by infection, they should likewise be excluded from the category of true tumors.

The above **classification of tumors** is based on their microscopic character and histogenesis.

Tumors are in no sense useful to the organism as many tissue-hypertrohies may be. Tumor-tissue does not possess the specific activity of that from which it springs. It happens, indeed, that in certain tumors there occur **processes** of **secretion** which correspond to normal secretions — epithelial tumors may produce mucous or horny or colloid material (thyroid tumors), or bile-pigment (liver-tumors), even in metastatic nodules — but from these facts we can conclude only that, in many tumors which do not differ too greatly in structure from the parent tissue, the cells may retain, to a certain degree, and for a number of generations, the functional capacities of the parent tissue. There is, however, no basis for believing that new useful tissue is formed as in the case of hypertrophy from increased labor; the products are for the chief part of no use to the body, and though perhaps in special cases the iodine-containing colloid produced by malignant tumors of the thyroid may be made use of, such a function must surely be of much less value than that of the normal tissue.

The tumors springing from the mesodermal epithelium of the serous membranes or of the glands arising from these, are included in the **group of epithelial tumors.** This is justified by the fact that such tumors correspond in their structure and clinical behavior to the epithelial tumors of the ecto- and entoderm. I have also considered the question whether it would not be advisable (as *Hansemann* has proposed) to class among the epithelial tumors — i. e., the adenomata and carcinomata — those tumors which have a framework of connective tissue, the spaces of which are filled, in a manner suggesting epithelial tissues, with cell nests arising from the proliferating endothelium of the blood- and lymph-vessels. Aside from the similarity in the structure of these tumors with the ordinary adenomata and carcinomata, there may be taken in favor of this view the anatomical fact that the endothelium of the blood- and lymph-vessels is often designated mesodermal epithelium. Against such a grouping of the endothelial with the epithelial tumors it may be urged that, aside from the general acceptance of the term endothelioma, the behavior of the endothelium of the blood- and lymph-vessels under pathological conditions is different from that of epithelium, and that in many tumors it is impossible to separate the products of the growth of the endothelium of blood- and lymph-vessels from the products of proliferation of connective-tissue cells.

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    See also §§ 100 and 101. For an admirable presentation of the entire subject of Tumors, see Ewing, Neoplastic Diseases, 1919.

§ 100. The **cause of tumors** is unknown. In the majority of cases, however, the *conditions* under which the new-growth appears can be assigned, and we may accordingly establish different groups.

In the first group may be included those tumors *arising from congenital local malformations of tissue*. They develop in uterine life, and are
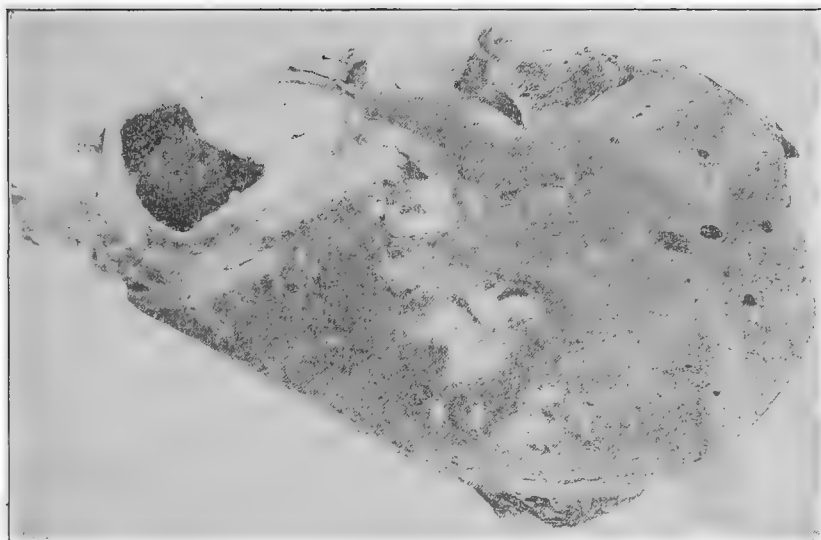
Fig. 212—(Bellevue Hospital.) Primary carcinoma of the gall-bladder with secondary infiltration of the substance of the liver, showing the presence of a large gall-stone in the lumen of the gall-bladder.

present at birth, or in extra-uterine life, during the period of growth or later, in which case trauma not infrequently gives the immediate occasion for the beginning of the tumor.

To this group belong many osteomata, chondromata, angiomata, gliomata, fibromata (of the nerves and skin), and adenomata. Further, many teratoid tumors and cysts are to be included, inasmuch as they represent either remains of fœtal structures, transpositions or monogerminal inclusions of embryonic tissue, implantations of rudimentary portions of a twin embryo (bigerminal implantations), or the results of disturbances of the earliest stages of the development of the ovum.

A *second group develops after traumatic injuries of tissues;* it has been reckoned that in about seven to fourteen per cent of cases a traumatic origin can be assigned; particularly in sarcoma, carcinoma, and osteoma. It may be a single injury, a stab, a blow, crushing fracture, etc., or repeated mechanical irritation, such as rubbing, etc.

In a third group the development of the tumor follows inflammation, particularly granulation tissue with subsequent cicatrization. The inflam-

mation and ulceration may be caused by non-specific as well as by specific agents. For example, cancer of the gall-bladder (Fig. 212), develops almost invariably only in gall-bladders which contain stones, and are consequently the seat of chronic inflammation. In the stomach, cancer may develop in the edge of an ulcer or in the resulting scar and also in a mucous membrane which has suffered severe changes as the result of previous inflammation. In the skin and in the mucous membranes of the pharynx and larynx cancers occasionally arise in the base of a tuberculous or syphilitic ulcer or in the scar of such a process.

In a fourth group the development of tumors appears to owe its origin to unequal atrophy of the elements which make up a tissue, so that certain hindrances to growth are removed or lessened. Not mechanical resistance alone, but influences dependent on chemical conditions, should be considered in this connection. Certain *epithelial proliferations (cancers)* develop in old age, or in organs which after a period of increased activity become atrophic. For example, the development of cancer of the skin may be explained on the ground that the connective tissue undergoes retrogression leading to relaxation, while the epithelium is still possessed of full power of proliferation. At the same time the chemical composition of the connective tissue may be altered.

It cannot be doubted that the **etiology of tumors** is not always the same, as shown by the variety of conditions under which they arise.

It is difficult to say what is the nature of the influence which excites the cells to the *production of an atypical tissue.* We are at first inclined to think of the same causes which underlie hypertrophy and regeneration of tissue, also of stimuli which increase the formative activity of cells, or of lessening or removal of hindrances to growth. But it still remains a problem why there should not be formed typical tissues which would so fit into the organization of the body that they would be of service. In the attempt to explain this phenomenon, many writers have sought and would recognize as the cause the presence of *parasites* (see Etiology of Carcinoma); but our present knowledge does not in any way justify us in attributing the development of true tumors to the influence of parasites. On the contrary, the development and life-history of tumors, and the formation of metastases, which arise through the multiplication of living tumor-cells transported in the lymph- or blood-stream, speak against the hypothesis of the parasitic nature of tumors.

Cohnheim advanced the theory that all true tumors arose from the persistence of foci of embryonal tissue. Neither the results of clinical observation nor of anatomical investigation speak in favor of such a theory.

Ribbert is of the opinion that the cause of the proliferation which leads to tumor-formation is to be found in separation of cells or cell-groups from their organic relations, such separation occurring as the result of intra-uterine disturbances of development or later under the influence of external agencies. Nevertheless, such transplantations or separations of cell-groups take place frequently in intra-uterine life, or after trauma, after ulceration, in scars and in infectious granulomata, without subsequent development of a tumor. These *transplantations of tissue constitute only one of the predisposing causes of tumor-formation;* some other factor is necessary to excite the atypical progressive tissue-proliferation — i. e., the development of the tumor. The *development of a tumor is, therefore, in no wise dependent upon transplantation of tissue; rather the tumor-proliferation takes its origin in cells which are normally situated;* this may be actually demonstrated particularly in epithelial tumors.

Our knowledge of the causes of tumor-development at the present time may be summed up as follows: Inherited and acquired conditions of certain cells and cell-groups, which assert themselves in a tendency to increased formative activity with the production of atypical tissue, lead to the formation of tumors. In many cases this proliferation is prepared for, favored, and excited by the transplantation of cells and cell-groups, but often also through changes in the neighborhood of the cells concerned. No general scheme applicable to the development of all tumors can be given. On the contrary, the conditions vary not only with the different forms of tumors, but with individual cases of the same tumor-type. Moreover,

it should not be forgotten that the formations which we class as tumors do not all possess the same significance, and that many more properly might be classed with other phenomena of growth (malformations).

§ 101. When once a **tumor** has arisen and has reached a certain stage of development it **may become quiescent,** and remain for a life-time without undergoing further change. This is true particularly of those which are regarded as *local tissue-malformations;* but tumors which
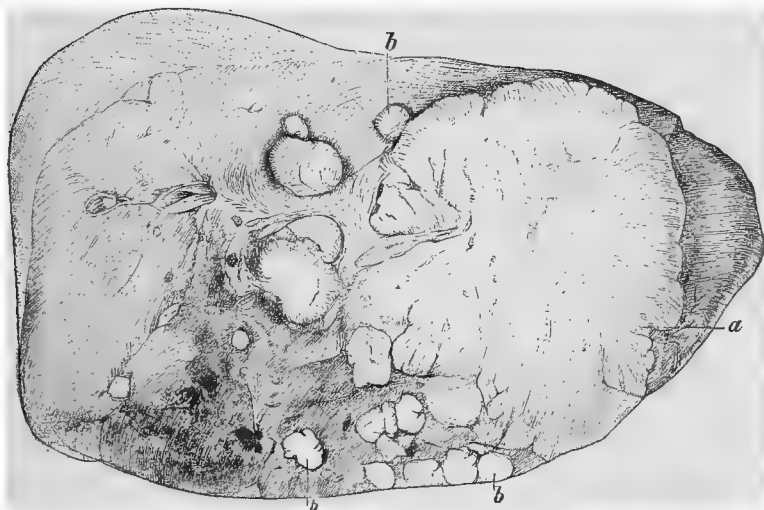
FIG. 213.—Section through primary cancer of the liver (*a*), with multiple metastases (*b*) within the liver itself. Three-sevenths natural size.

first develop in later life may come to a standstill after attaining a certain size.

The **growth of a tumor takes place independently,** and in many cases continues until death.

From the surrounding tissues the tumor acquires its blood-vessels and hence its food material, but may besides grow independently — i. e., through increase of the cells which form the elements of the tumor. In many cases the tumor increases in size through **interstitial expansive growth,** and the neighboring tissue is crowded or pushed aside. In other cases the **tumor grows by infiltration** and *forces its way into the intercellular spaces of the neighboring tissue,* so that new areas are brought under the influence of the tumor. In this way the cells of the invaded tissue are often excited to proliferation, and enlargement takes place through *appositional growth.*

The characteristic feature of **growth by infiltration** consists in *involvement of the tissues of the organ* that lie in the neighborhood of the primary tumor. Further, the *tissue of neighboring organs may become involved by the tumor* through *contiguity.* If *tumor-cells gain entrance into the great body-cavities they may spread over the serous surfaces and lead to the development of secondary tumors.*

If, in the process of infiltration, a tumor *gains entrance to a lymph- or blood-vessel* — an event which is likely to occur in carcinoma and sarcoma — and *if tumor-cells capable of proliferation* are transported through the lymph or blood, **tumor-metastases** arise — that is, secondary or **daugh-**
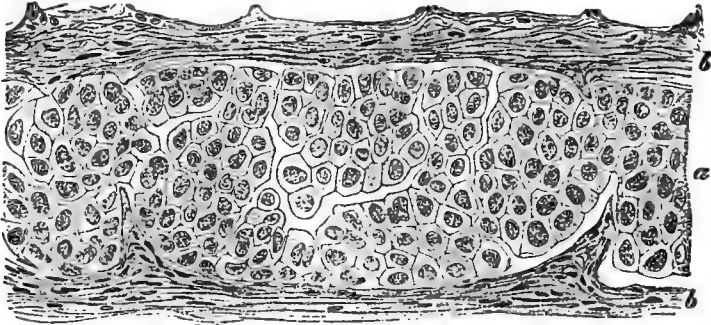
FIG. 214.—Periglandular lymph-vessel (in the axillary region) filled with cancer-cells arising from a primary carcinoma of the mammary gland (Müller's fluid, hæmatoxylin). *a*, Cancer-cells; *b*, wall of lymph-vessel. × 300.

ter tumors which are not directly connected with the original focus of growth. The daughter-tumors may develop first in the organ primarily affected (Fig. 213, *b*), but usually involve other organs as well; in the case of rupture into lymph-vessels the *lymph nodes* are first affected; in rupture
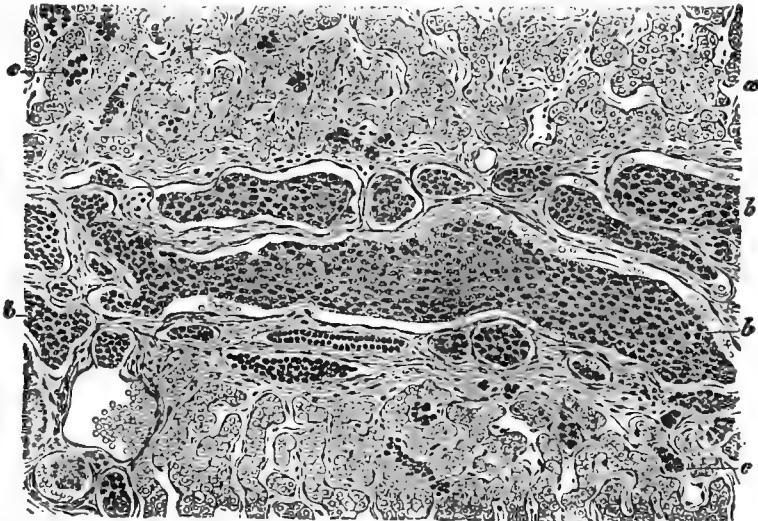
FIG. 215.—Metastatic development of cancer in the branches of the portal vein and liver-capillaries (Müller's fluid, hæmatoxylin, and eosin). *a*, Liver tissue; *b*, plugs of cancer-cells in the portal vein; *c*, cancer-cells in the capillaries. × 100.

into blood-vessels, *those organs to which the blood carries the living cells.* The direction of transportation is usually that of the lymph- or blood-stream, but retrograde transportation not infrequently occurs, particularly in the lymph-vessels, the lumina of which are easily obstructed by tumors.

The development of daughter-tumors takes place from transported cells. In lymphatic **metastasis the lymph-vessels** (Fig. 214, *a*) are invaded by tumor-cells which are deposited at a distant point, this is followed by proliferation and metastatic nodules develop. It not infrequently happens that the *lymph-vessels are uniformly distended by the growth* (Fig. 214, *a*), without the formation of nodules, or at least only small swellings develop along the course of the lymph-vessels. In metastasis into *lymph nodes* the latter become swollen, forming *nodules* of smaller or larger size,
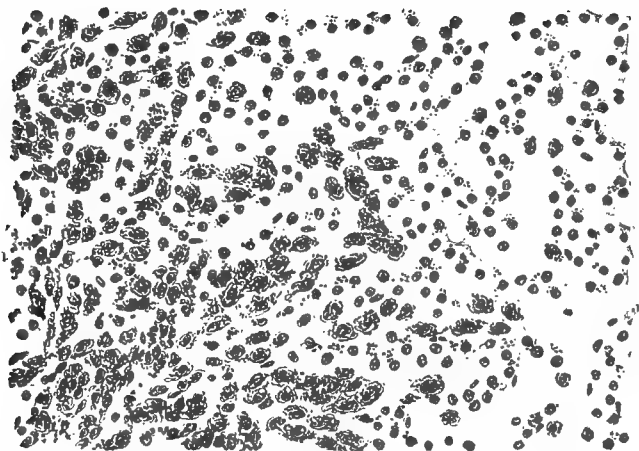
Fig. 216.—Metastatic sarcoma of the liver from a primary sarcoma of the parotid (Flemming's solution, safranin, picric acid). *a*, Liver-rods; *b*, sarcoma tissue developing within the vessels; *c*, isolated tumor-cells in the liver-capillaries; *d*, liver-cells which have undergone atrophy and fatty degeneration. × 150.

and the structures of the node are gradually replaced by tumor tissue.

In **metastasis through blood-vessels** the development of the secondary tumor begins with the deposit of tumor-cell emboli in artery, capillary, or vein, and the vessels (Figs. 215, *b, c;* 216, *b, c*) may eventually be filled and dilated by proliferating tumor-cells. The tissue in which the tumor-embolus develops may remain passive, and the specific tissue-elements — gland-cells (Fig. 216, *d*) and muscle-cells — may vanish as the result of pressure atrophy. Later, the blood-vessels and connective tissue may take part in the development of the secondary tumor.

In the further course of development the secondary nodule is usually sharply circumscribed from its surroundings and grows by expansion. It not infrequently happens, however, that the infiltrative growth persists, and under these conditions widespread diffuse tumors develop, particularly in the bone-marrow and the liver (Fig. 216).

The number of lymphogenous and hæmatogenous metastases varies greatly in different cases. At one time the metastases may be confined to one organ, at other times they may be scattered through several. In rare cases cells of the original tumor may be spread through the entire body, so that in diverse organs — glands, muscles, skin, etc. — larger and smaller nodules appear in quick succession. This phenomenon is possible when tumor-nodules break into blood or lymph vessels and the tumor cells are thus enabled to spread throughout the body and to lodge and grow in different parts (carcinomatosis, sarcomatosis, melanomatosis, etc.).

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If a living bit of tumor (carcinoma, sarcoma) capable of forming metastases is transplanted from one animal into the tissues of another animal of the *same species,* it sometimes happens that it will develop in the second animal. In man, tumor particles may be transplanted during operations from one part of the body to another and there grow (implantation metastasis), or rupture of an encapsulated tumor may be followed by secondary implantations in neighboring surfaces, e. g., in certain ovarian tumors rupture may be succeeded by extensive implantation metastases in the peritoneum.

Side by side with progressive proliferation of tissue there frequently occur in tumors **retrogressive changes,** particularly in rapidly growing and infiltrating cellular tumors, in which fatty and mucous degeneration, necrobiotic processes, and hæmorrhages may take place to such marked degree as to bring about extensive *destruction of the tumor tissues.* This disintegration is due to the fact that the tumor grows into or compresses the blood-vessels and obstructs them. If the cells are badly nourished they undergo necrosis and become dissolved through the action of proteolytic ferments. In nodular tumors the destruction of tumor-cells, followed by softening or partial resorption of the products of degeneration, leads to local areas of *umbilication.* Often *ulcers* may thus be formed; in carcinomatous tumors of mucous membranes the parts growing above the surface often undergo disintegration. In slowly growing tumors of hard consistence extensive retrograde changes do not usually occur.

The necrosis and disintegration of a tumor rarely terminate in **cure.** This event is most likely to happen when a polypoid new-growth becomes totally necrotic (for example, as a result of twisting or tearing of its pedicle) and is thrown off. In the majority of tumors showing a tendency to retro-

Fig. 217.—Recurrent sarcoma in the amputation-stump of the femur. *a,* Fungoid tumor arising from the bone-marrow; *b,* periosteal nodules; *c,* metastasis. One-half natural size.

gressive changes and disintegration, while the older portions are dying the growth advances at the periphery, and new tissues are progressively attacked.

If the **tumor is completely extirpated, cure** may be brought about. This is most easily accomplished in slowly growing and sharply circumscribed tumors which increase by expansion. In infiltrating tumors it is difficult to determine the boundary of the growth, since this may extend far beyond the point where macroscopic change is apparent. Consequently, in such cases, **recurrence** sooner or later takes place in the scar, and (Fig. 217, *a*) arises from portions of the tumor remaining in the tissues. Such recurrences behave exactly like the primary tumor, and may

form metastases (Fig. 217, *c*). In those cases in which recurrence in the scar following operation is long delayed, it is possible that this circumstance depends on the fact that in the affected area the *conditions favoring tumor development again occur.*

According to their clinical and anatomical characteristics **tumors** may be classed as **benign** and **malignant.** *Benign tumors* are generally regarded as those *which grow slowly and by expansion and do not form metastases; malignant, those which show complete emancipation from the normal laws of proliferation, grow quickly and by infiltration, easily undergo degenerative changes and form metastases.*

The **malignant tumors,** on the whole, coincide with those forms which are known as *carcinoma* and *sarcoma.* It must, however, be borne in mind that the malignancy of a tumor depends not only on its character, but also on its location (*local malignancy*). A benign tumor takes on malignant character as soon as its presence interferes with the functions of vital organs. Hence every tumor of the brain or meninges becomes a dangerous affection at the moment when it gives rise to disturbances of the cerebral functions. Under certain conditions such benign tumors as fibromata of the uterus become destructive, or locally malignant, as soon as they reach such size as to displace and compress neighboring organs.

After a tumor has existed for a certain period there frequently results marked lowering of the general nutrition, marasmus, which is designated **tumor-cachexia.** This occurs oftenest in association with the malignant growths known as cancer and sarcoma; and may depend, in part at least, on the great demands made on the food supply by the rapid growth of the tumor, particularly if there are metastases. A still more important cause may be that the tumor interferes with the ingestion of food. In cancer of the œsophagus, stomach, and intestine the function of the affected organ is interfered with, and the entrance and assimilation of food may be entirely prevented or nearly so. Further, it should be borne in mind that through degeneration of the tumor and from resulting ulcers large amounts of albuminous material are lost; and that through putrid decomposition there may arise substances which, when absorbed, act injuriously on the organism. Finally, the pain which is often felt in a tumor may rob the patient of sleep. Whether the tumor itself produces substances harmful to the organism is unknown, but is, however, not improbable.

Metastases occasionally occur with **benign tumors,** chondromata, myomata, and adenomata. Of these, the metastases in the bones of thyroid tumors are of special importance; they occur when no carcinomatous proliferation can be demonstrated in the thyroid, so that it would seem probable that under certain conditions even the cells of a normal or hypertrophic tissue may be transported into the bone-marrow and there proliferate.

II. The Different Forms of Tumors.

I. Tumors Derived from Connective Tissue or the Supporting Framework.

(a) *Fibroma.*

§ 102. A **fibroma** is a tumor composed of *fibrous connective tissue.* It occurs most frequently in the form of *nodules,* which are sharply circumscribed from the surrounding tissues, and usually involve but a portion of the affected organ. Rarely an entire organ (ovary) may become

changed into a single tumor-mass. On a free epithelial surface and on mucous membranes a fibroma may appear in the form of a *papilloma* or *polyp.*

According to the character of the connective tissue of which it is com-posed, the consistence of a fibroma may vary greatly. Often it is *hard* and *tough,* creaking under the knife, and showing on its surface a white, tendon-like, shining tissue (*desmoid*) ; but in other cases the growth may be soft, flaccid, the cut surface more uniformly grayish-white and somewhat translucent. In still other cases the individual strands of connective tissue are white and shining, but the tumor as a whole has a looser structure and is correspondingly flaccid.

Between the hard and soft growths there are all possible transition-forms, and even in one tumor different parts may possess different characteristics. Under the microscope the hard fibromata appear to be composed chiefly of thick

Fig. 218.—Hard fibroma from lobe of the ear (alcohol, hæmatoxylin), *a,* Longitudinal section; *b,* transverse section of bundles of fibres. × 400.

bundles of coarse fibres (Fig 218, *a, b*), in which lie scattered a larger or smaller number of cells. In the softer forms the bundles of fibres are more delicate (Fig. 219, *a*). If as a result of congestion or other cause clear fluid collects between the fibrillæ, there is formed an *œdematous fibroma,* whose bundles of fibres (Fig. 219, *b*) are pressed apart by the fluid, the tumor becoming softer and more translucent, finally resembling the tissue of the umbilical cord.

Fig. 219.— Section of an œdematous fibroma of the uterus (osmic acid, glycerin). *a,* Closely lying fibres; *b,* fibres pressed apart by fluid; *c,* spindle-shaped cells; *d,* swollen round cells; *e,* blood-vessel. × 200.

The *soft fibroma,* which presents a translucent, grayish-white cut surface, is usually rich in cells; so that it is possible by teasing to isolate numerous slender spindle-shaped forms with terminal fibrils. The intercellular substance is correspondingly less in amount, the fibrillæ more delicate and arranged in finer bundles. Sections of such fibromata, when stained, appear rich in nuclei (Fig. 220, *b*).

Fibromata develop from proliferating connective-tissue cells, and it is usually possible to find in the tumor areas which are richer in cells than others, and in which the cells appear not only as small spindle cells, but as round cells, or as short, thick spindles, or even as stellate cells. The transformation of the newly formed cellular tissue into connective tissue takes place in the same way as that described under Hyperplasia of Connective Tissue. New-formation of elastic fibres is usually wanting, but

at times does occur, particularly in the neighborhood of the blood-vessels.

Fibromata may appear in any part of the body which contains any form of connective tissue. They occur most frequently in the nerves, skin, periosteum, fascia, mammæ, and mucous membrane of the nose; more rarely in the ovary, intestinal tract, etc. In the mammary gland the development of the fibroma takes place particularly around the canaliculi (Fig. 220, b), which become surrounded by connective tissue rich in cells.

Fibromata do not form metastases, but often occur as multiple tumors, especially in the nerves and skin (see Neurofibroma, § 111). Moreover,
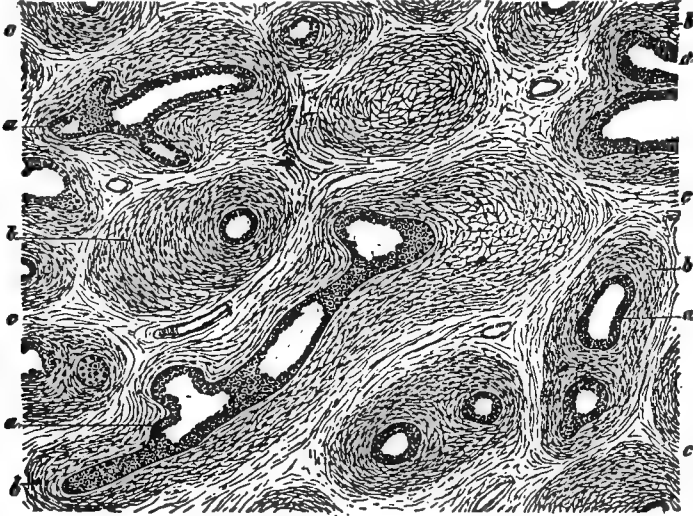
Fig. 220.—Fibroma pericanaliculare mammæ (Müller's fluid, alum carmine, eosin). a, Gland-tubules; b, newly formed pericanalicular connective tissue rich in cells; c, connective tissue poor in cells. × 35.

it is not uncommon to see in a tumor several centers of growth — that is, the mass of the tumor is made up of several nodules or bands held together by ordinary connective tissue (Fig. 220, b). Fibromata are malignant only through size and position.

Fibromata may undergo mucous or fatty degeneration or may soften and disintegrate, so that cavities are formed in them. They may also break down and give rise to ulcers. Their blood-supply varies greatly, at times being scanty, at other times abundant. Occasionally the blood-vessels are ectatic, so that the tissue is interspersed with wide channels and clefts, from which blood escapes when the tumor is incised and examined in the fresh state. In other cases dilated lymph-channels are seen.

Keloid is the designation applied to a hard, nodular, or flat and banded, or stellate growth of the skin, which in its fully developed state consists of dense fibrous tissue without elastic fibres. The direction of the fibres is often at right angles to the surface of the skin, or at least does not accord with that of the normal fibres. It usually develops after injuries or inflammations (*cicatrix-keloid*), but may appear without such association (*spontaneous keloid*). The cause of keloid growth is not known; the tendency to recurrence after removal, the multiple occurrence,

and the fact that cases frequently occur in the same family (Hutchinson) speak in favor of some special predisposition on the part of the skin.

(b) Myxoma.

§ 103. A **myxoma** is a tumor which consists essentially of *mucous tissue,* and is made up of cells and a fluid or gelatinous intercellular substance containing mucin. The cells are for the greater part polymorphous, with processes of varying length (Fig. 221) which anastomose with one another (Fig. 222, *a*). The tissue is markedly translucent, soft and the blood-vessels are easily seen through it. From the cut surface gelatinous or stringy masses which swell in water, may be obtained.

No tumor is ever made up wholly of myxomatous tissue; the latter is usually combined with other forms of tissue, particularly with fibrous connective tissue, fat tissue, cartilage, and sarcomatous tissue. For this reason such tumors are designated **fibromyxoma, lipomyxoma** (Fig. 224), **chondromyxoma** (Fig. 227, *c*), and **myxosarcoma** (Fig. 222).

Mucous tissue may develop from fibrous connective tissue through the collection of a mucin-containing fluid between the fibrillæ and the gradual disappearance of the latter. Adipose tissue may pass over into myxomatous tissue through the disappearance of fat from the fat-cells and the appearance of a mucin-containing gelatinous substance between the cells, during which process the fat becomes broken into droplets (Fig. 224, *b, c*), while the cells themselves become smaller and star-shaped (*d*). Cartilage may also become transformed into mucous tissue through mucoid degeneration of the basement-substance and change of form of the cells (Fig. 227, *c, d*). Myxosarcomata (Fig. 222) arise either through local increased activity

FIG. 221.—Cells from a myxoma of the periosteum of the femur (gold preparation). × 400.

of cell-proliferation in myxomata or through a collection of mucoid substance between the sarcoma cells.

Myxomata, myxofibromata, and myxolipomata develop most frequently in the connective tissue of the periosteum and endosteum, skin, heart, fascia, and sheaths of the muscles, as well as in the fat tissue of the subcutaneous and subserous tissues. Myxochondromata occur particularly in the parotid, and constitute the most common form of tumor found there.

These forms are all benign tumors, which rarely produce metastases. Myxosarcomata, on the other hand, have characteristics of malignancy, and may form metastases.

(c) Lipoma.

§ 104. A **lipoma** is a tumor consisting of *adipose tissue* (Fig. 223). These tumors are sometimes soft, almost fluctuating, sometimes firm, usually nodular and lobulated, and often attain great size.
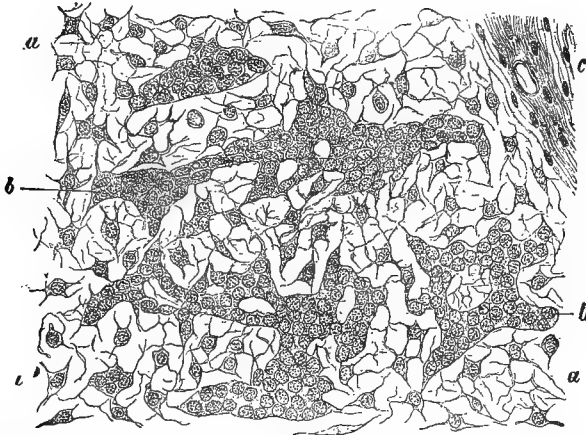
FIG. 222.—Section of a myxosarcoma (Müller's fluid, carmine, glycerin). *a*, Myxomatous tissue; *b*, strands of cells; *c*, fibrous tissue. × 225.

Histologically, the tissue of a lipoma resembles the fat-lobules of the subcutaneous panniculus (Fig. 223), although the tendency to form typical grape-like clusters of fat-cells is wanting. If, as not infrequently happens, mucous tissue is formed in connection with the fat tissue, or if

FIG. 223.—Lipoma of shoulder region, with relatively small fat-cells (Müller's fluid, hæmatoxylin). × 300.

the latter, following disappearance of its fat, becomes changed into myxomatous tissue, the tumor is designated **lipomyxoma** (Fig. 224); if there is an abundance of fibrous tissue present, it is called **lipofibroma** or **fibrolipoma**.

Calcification, necrosis, gangrene, and sloughing are not infrequent in lipomata of large size. These tumors do not produce metastases, but are often multiple. Complete disappearance of a lipoma does not take place even in extreme emaciation of the host.

Lipomata are sometimes observed in new-born children — for example, as tumors developing in or over the cleft-formations of spina bifida — but occur much more frequently in later years. The most common seats of these growths are the subcutaneous tissues of the back, buttocks, neck, axilla, abdomen, and thigh; they are also found in the intermuscular

connective tissue, subserous fat tissue, in the kidneys, intestine, mammary gland, under the aponeurosis of the forehead, in the skin, fingers, joints, etc. They may occur as multiple growths symmetrically distributed. In man the formation of fat tissue about the neck and throat, leading to
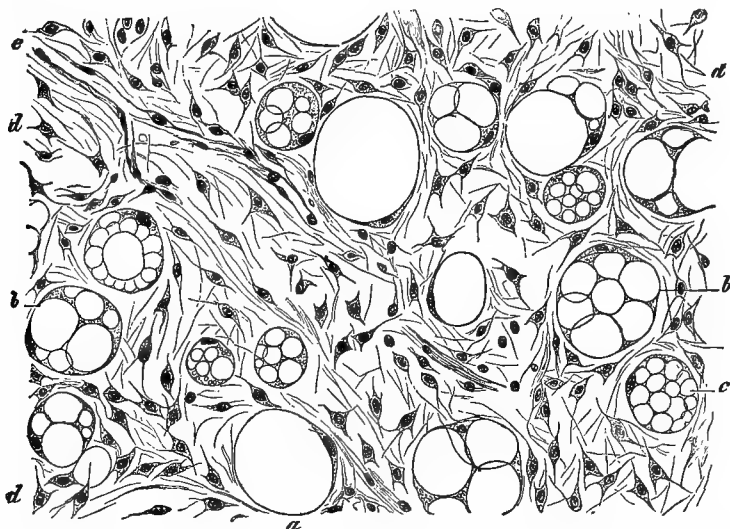
FIG. 224.—Lipomyxoma of the back (Müller's fluid, Van Gieson's). *a*, Large fat-cells; *b*, *c*, fat-cells in which the fat is broken up into little droplets; *d*, mucous tissue; *e*, blood vessel. × 300.

nodular and lobulated disfigurations of this region, occasions the designation *fatty collar*. The development of fat in these cases takes place in the subcutaneous tissue, in and under the fascia and between the muscles. Abnormal development of fat in an extremity may give rise to the condition known as *lipomatous elephantiasis*.

There are at least two other varieties of lipomatosis that deserve mention, namely, **Dercum's syndrome and that of Frölich.** The former, known as *adiposis dolorosa,* is characterized by symmetrical deposits of fat in various parts of the body, preceded or attended by pain and sometimes associated with asthenia and mental disturbances. The lipomatous masses involve the abdomen, chest, arms or legs, or may be localized on the limbs or trunk. The affection is more common in females. The few cases which have been investigated post-mortem have shown, among other things, in addition to the lipomatosis, interstitial neuritis, changes in the thyroid gland and sometimes in the pituitary. The *syndrome* of *Frölich* or *dystrophia adiposo-genitalis* is a condition of obesity which occurs in connection with tumors of the pituitary and is associated with hypoplasia of the genital organs and infantilism. Lyon (Archives of Internal Medicine, 1910) has contributed an admirable paper on the subject of lipomatosis. He includes (1) *Dercum's syndrome,* (2) *simple adiposity,* (3) *solitary multiple or symmetrical nodular circumscribed lipomatosis,* (4) *diffuse symmetrical lipomatosis,* including the so-called "fat neck," (5) *neuropathic œdema, pseudo-œdema* and *pseudo-lipoma,* and (6) *the syndrome of Frölich.* He believes that all of these conditions are merely different expressions of the same morbid process.

In addition to the forms already described, there are lipomata composed of proliferating embryonal fat cells which display a disposition to invade surrounding tissues and thus to become diverted in the direction of malignancy. Still another but rare variety of lipoma consists in a combination of adult and embryonal fat cells supported in a reticulum of connective tissue and associated with the presence of collections of newly formed or dilated capillary or other small vessels (*lipoma*

cavernosum). A patient at Bellevue Hospital presented these growths in the subcutaneous tissue literally by dozens.

There is a large group of chronic productive inflammatory lesions characterized by the infiltration of greater or less numbers of embryonal fat cells. *Sometimes these are so numerous and so closely packed or so widely distributed through the tissues as to suggest neoplasmic transformation.* Such changes are not uncommonly encountered in productive inflammatory lesions in the breast, the walls of the gall-bladder and intestine, the interstitial tissues of the bone marrow, occasionally in the kidney in chronic interstitial nephritis and particularly in tissues which are normally rich in fat, such as the omentum and mesentery (Symmers and Fraser, Arch. Internal Medicine, 1917).

Extensive hyperplasia of embryonal fat cells is sometimes to be seen in *marantic infants*. In such a case investigated by myself at the New York Hospital, embryonal fat cells occurred in such enormous numbers as to suggest the presence of a new growth. They were distributed, however, through those regions where fat is normally encountered and consisted of bright cherry-red nodules composed of embryonal fat cells lying in a network of capillary vessels.

(d) Chondroma.

§ 105. A **chondroma** or **enchondroma** is a tumor consisting essentially of *cartilage*. The amount of connective tissue covering its surface or accompanying the blood-vessels into its interior, is so slight as to fall completely into the background when compared with the cartilage.

Chondromata develop chiefly in those places where cartilage is normally found — that is, in the osseous system or in the cartilages of the respiratory tract; but also occur in tissues which normally possess no cartilage —
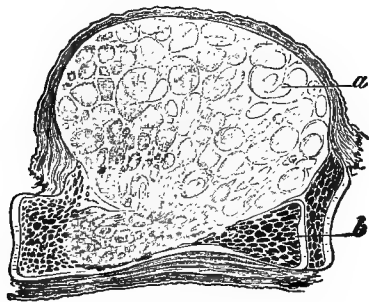
FIG. 225.

FIG. 226.

FIG. 225.—Periosteal chondroma of a digital phalanx, seen in longitudinal section. a, Chondroma; b, phalanx. Natural size.
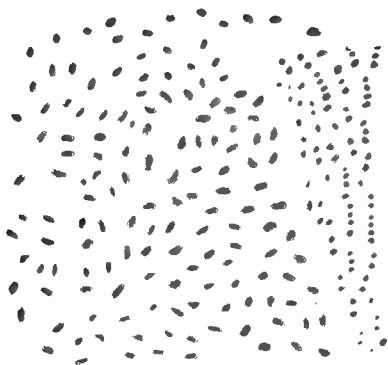
FIG. 226.—Section from a chondroma of the ribs (hæmatoxylin, carmine). a, Cartilage rich in small cells; b, cartilage rich in large cells. × 80.

for example, in the salivary glands, particularly the parotid, and in the testicles, rarely in other organs. In bones which develop from cartilage, chondromata arise from cartilaginous remains that persist after ossification; but more often take their origin from the periosteum and endosteum (Fig. 225). They form tumors which vary greatly in size. The small ones are usually spherical (Fig. 225); the larger ones nodular or lobulated. The individual nodules are often separated from one another by connective tissue. Not infrequently they are multiple, particularly in the skeleton, where they sometimes may be found literally by dozens.

The tissue of an enchondroma most often presents the characteristics of hyaline cartilage (Fig. 226), more rarely that of reticular or fibrous cartilage. At the periphery of the tumor the cartilage passes over into connective tissue, which forms a kind of perichondrium.

The number, size, form, and grouping of the cartilage cells vary greatly in different cases and in different parts of the same tumor. Many enchondromata are cellular (Fig. 226), others poor in cells, many contain large cells, others small cells, or both large and small cells.

The cells are sometimes surrounded by a so-called capsule, at other times not; sometimes they lie in groups inside the mother-capsule, at other times they are more regularly distributed. All varieties of cartilage normally occurring in the body are found in
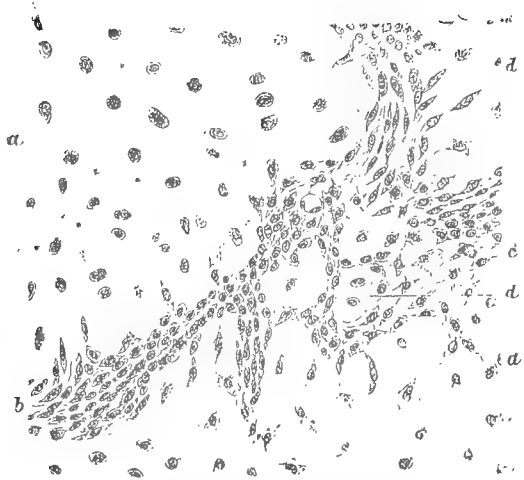
Fig. 227.—Chondromyxosarcoma parotidis (alcohol, carmine). a, Cartilage; b, sarcomatous tissue; c, myxomatous tissue; d, cartilage in process of liquefaction and being converted into sarcomatous and myxomatous tissue. × 80.
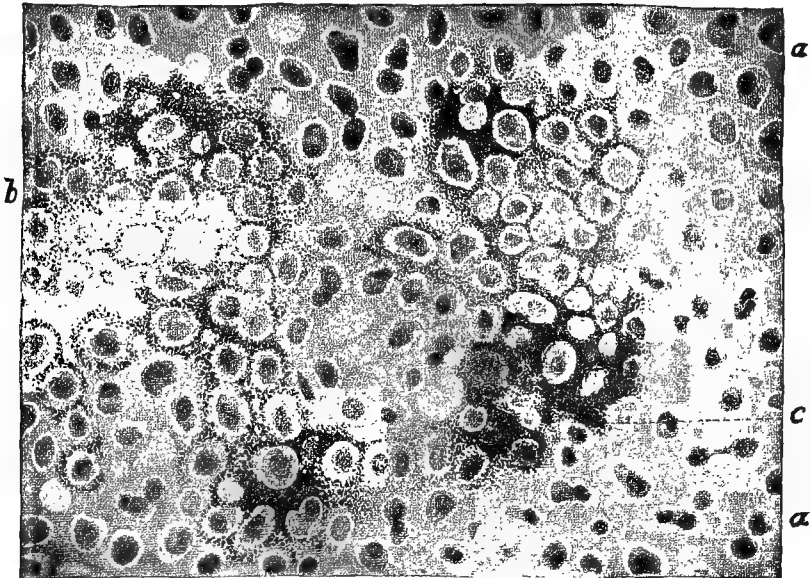
Fig. 228.—Periosteal chondroma of the calcaneus, with areas of calcification (Müller's fluid, hæmatoxylin). a, Hyaline cartilage; b, c, calcified cartilage. × 225.

enchondromata. Accordingly the cells vary in form; the majority showing the familiar spherical form, but spindle and stellate cells are not rare, particularly in the neighborhood of the connective-tissue bands
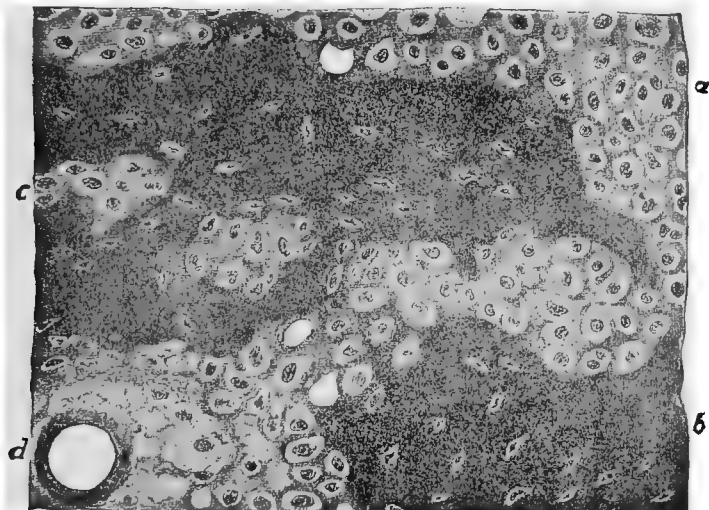
Fig. 229.—Osteochondroma of the humerus (alcohol, picric acid, hæmatoxylin, carmine. *a*, Hyaline cartilage; *b*, bone; *c*, cartilage which is becoming converted into bone; *d*, blood-vessel. × 250.

which divide the tumor into nodules or surround it as a whole. Cartilage, the perichondrium, endosteum, periosteum, and different forms of connective tissue may form the matrix of enchondromata. Chondromata arising from the surface of cartilage or bone are known as *ecchondroses.*

Fig. 230.—Ivory-like exostosis of the parietal bone. Natural size.

The tissue of enchondromata frequently suffers retrogressive metamorphoses. The ground-substance in large tumors shows a tendency to undergo, in localized areas, mucoid degeneration and liquefaction, the first (Fig. 227, *c*), giving rise to *chondromyxoma,* liquefaction of the ground-substance with destruction of cells forming cyst-like collections of fluid. In other cases the cartilage may become calcified Fig. 228, *b, c*), or true *bone* may be formed (Fig. 229, *c, b*), so that the tumor must be termed an **osteochondroma.** Through marked proliferation of cartilage cells *sarcomatous tissue* may be developed, the tumor becoming changed to a **chondrosarcoma** (Fig. 227, *b*).

The enchondromata are, on the whole, benign tumors, although metastases are not unknown.

In the region of the spheno-occipital suture, in the median line of the clivus, there is not infrequently found a small tumor which either lies beneath the dura, or at its highest point breaks through this membrane and penetrates into the arachnoid and pia. The tumor consists of bladder-like cells, resembling plant-cells. Cartilage and bone tissue may be associated with the peculiar tumor tissue, and for this reason *Virchow* regarded the growth as a chondroma arising from remains of the spheno-occipital cartilage and characterized by vacuolar degeneration of the cells. The peculiar character of the tissue, however, favors the view advanced by *Müller,* and supported by *Ribbert,* that the growth is a product of proliferative activity of remains of the notochord, and the tumor has consequently been designated chordoma. *Ribbert* states that chordomata of small size are to be found in 2 per cent of all routine autopsies. At Bellevue Hospital we have never detected such a growth in over 6,000 autopsies.

(e) Osteoma.

§ 106. The term **osteoma** is applied to tumors which consist of *osseous tissue.* Such growths arise chiefly from the bones of the skeleton (Figs. 230, 231), but may develop elsewhere.

FIG. 231.— Exostosis cartilaginea of the upper diaphysis of the tibia. Reduced about one-half.

A small circumscribed new-growth of bone attached to old bone is called an *osteophyte;* when of a large size an *exostosis.* Circumscribed formations of bone inside of bones are known as *enostoses.* New-growths of bone not attached to old bone are classed as follows: *movable periosteal exostoses,* which have their seat in the periosteum but are separated from the bone; *parosteal osteomata,* lying near the bone; *disconnected osteomata,* which are situated some distance from the bone, in the muscles, and tendons; and, finally, *heteroplastic osteomata,* which occur in other organs, in the lungs, mucous membrane of the trachea, in the skin, arteries, mamma, etc.

Excrescences on the teeth, consisting of cement-substance, are known as *dental osteomata;* those consisting of dentine, as *odontomata.*

According to their structure, osteomata may be divided into hard *osteomata* (*osteoma durum*) (Fig. 230) and *spongy* forms (*osteoma spongiosum* or *medullare*) (Figs. 231, 232). The former consist of firm, compact tissue resembling the cortical portion of long bones, and possess narrow nutrient canals; the latter are made up of delicate bony

trabeculæ and wide medullary spaces (Fig. 232), and resemble the structure of spongy bone.

The surface is sometimes regular and smooth, and the tumor presents the form of a cone (Fig. 230), sphere, or pedunculated button; or it may be rough, and nodular, without resemblance to form (Fig. 231). The first variety occurs most frequently as exostoses on the skull (Fig.
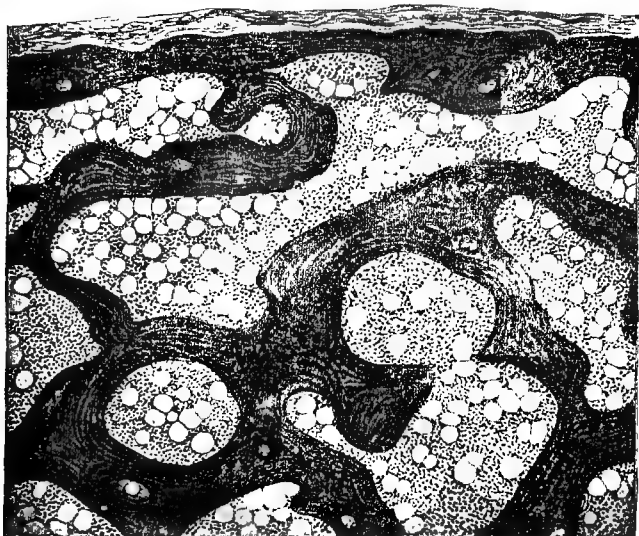
FIG. 232.— Osteoma of the dura mater (alcohol, picric acid, hæmatoxylin, carmine). × 40.

230); the latter as spongy exostoses and disconnected and heteroplastic osteomata, such as are sometimes encountered in the falx of the dura mater (Fig. 232).

Osteomata may occur as *single* or *multiple tumors,* the latter being relatively common. The ivory-like exostoses of the cranium and the osteomata of the dura mater are frequently multiple, and circumscribed bony growths often appear in great numbers on the bones of the extremities and trunk. In such cases the epiphyseal ends of the bones and the points of insertion of tendons, or both, are favorite sites. It is probable that such growths are to be referred to an inherited predisposition of the part to over-growth, or to disturbances in the development of the skeleton. The bony plates and spicules, which occasionally develop in the lung or in the mucous membrane of the air-passages, may occur in large numbers..

The development of bone in osteomata and osteoid growths takes place partly through osteoblasts, as described in § 83, and partly through metaplasia of formed tissues (§ 88). The matrix is formed from the connective tissue of the periosteum, or from that of the tissue from which the osteoma arises; or from the perichondrium or endosteum. If an exostosis develops in such manner that cartilage is formed from the proliferating periosteum or endosteum and if from this cartilage bone is developed, it is called a *cartilaginous exostosis* (Fig. 231); when the exostosis is formed directly from the proliferating periosteum without an intermediate stage of cartilage, it is known as a *connective-tissue exostosis* (Figs. 230, and 232).

The combination in the same tumor of connective tissue and bone in relatively equal proportions is known as an **osteofibroma.** This is a common tumor of the osseous system. The abundant production of bone in a chondroma leads to the formation of an **osteochrondroma** (Figs. 229, and 233) ; these tumors are usually found in the long bones. The new-growth may develop in the periosteum (Fig. 233, *c*) or endosteum (*a*, *b*). Abundant formation of bony trabeculæ (*f*, *h*, *k*) in the cartilage (*e*, *g*, *i*) gives to the tissue a hard consistence.

Many new-growths of bone are not tumors in the strict sense, but malformations of the skeleton resulting from excessive growth, or inflammatory hyperplasias. Many osteophytes and exostoses, parostoses and the disconnected osteomata (bone formation in lymph-n o d e s a n d lungs) are best interpreted as malformations. The bony plates not infrequently found in the falx of the dura, and which have a normal bone-marrow (Fig. 232), are to be regarded as misplaced portions of the skeleton. According to Ziegler the formations known as *rider's bone* and *drill-bone*, which are found in the adductors of the thigh

FIG. 233.—Osteochondroma of the humerus (alcohol, picric acid, hæmatoxylin, carmine). *a*, Cortical portion of the humerus; *b*, medullary cavity; *c*, periosteal deposit of bone; *d*, normal Haversian canals; *e*, dilated Haversian canals filled with cartilage, containing newly formed bone at *f*; *g*, cartilage with bone-trabeculæ *h*, formed by the periosteum; *i*, cartilage with newly formed bone-trabeculæ, arising from the endosteum; *k*, *l*, old bone trabeculæ; *m*, remains of marrow-tissue. Pocket-lens magnification.

and in the deltoid muscle, as the result, respectively, of riding and the repeated shouldering of arms, are to be regarded as tumors which arise on a congenital basis, in that the connective tissue of the muscle shows characteristics which ordinarily belong only to the periosteum and bone-marrow. The so-called *myositis ossificans* — a peculiar disease of the muscles, characterized by progressive ossification of their connective tissue during childhood — is to be similarly interpreted.

There are two varieties of *ossifying myositis* — one local, the other widespread and progressive. The local variety, as already indicated, is associated with frequently repeated injuries, but occasionally follows single blows or other mechanical influences, producing rupture of muscle fibres succeeded by hæmorrhagic and exudative inflammation. This gradually goes over into a chronic productive lesion attended by proliferation of the interstitial connective tissue which then, through a process of metaplasia, becomes transformed into bone. The progressive variety of

myositis ossificans is extremely rare and involves groups of muscles in various parts of the body leading, in advanced cases, to almost complete locking of the skeleton.   The majority of cases are associated with congenital malformations of various sorts, notably supernumerary fingers and toes, microdactyly, dwarfing of the lower jaw, etc.   Histologically this form is likewise characterized by overgrowth of the connective tissues between the muscles, followed by metaplasia into bone.

There is a well defined clinical condition attended by the appearance of multiple exostoses in various parts of the body, sometimes to the extent of dozens or even hundreds.   These exostoses are most frequently found in the growing ends of diaphyses of long bones where membrane and cartilage formation come into juxta-position.   Arthur Keith, who has carefully studied the condition, believes that it should be removed from the category of tumors, the exostoses being secondary formations which serve to mask a remarkable disorder of growth characterized by the fact that, as bone is being laid down within the growth disk in the epiphyseal line in cartilage, a covering of fibroblastic bone is being deposited by the overlying periosteum.   Keith suggests that the condition be placed among the disorders of growth known as diaphyseal aclasis.

(f) Hæmangioma and Lymphangioma.

§ 107. Under the term **angioma** are grouped *tumor-like formations in which blood-vessels* or *lymph-vessels constitute the striking feature.*

Vascular growths arising from blood-vessels are called **hæmangiomata,** or *angiomata* in the restricted sense; those arising from lymph-vessels are
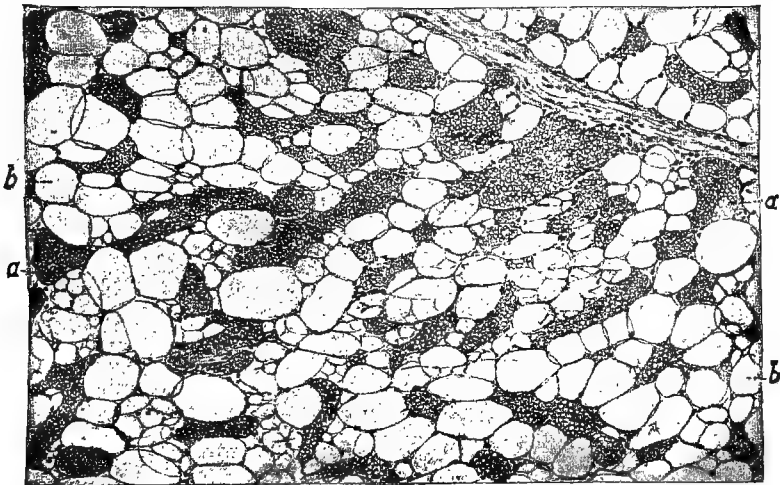
FIG. 234.—Teleangiectasis of the panniculus adiposus of the abdominal wall (formalin, hæmatoxylin, eosin).   *a,* Blood-vessels filled with blood; *b,* adipose tissue.   × 80.

designated **lymphangiomata.**   Of the hæmangiomata there may be distinguished four varieties: *hæmangioma simplex, hæmangioma cavernosum, hæmangioma hypertrophicum,* and *angioma arteriale racemosum.*

Hæmangioma simplex is a vascular formation in which, in a ground tissue of normal occurrence in the body, there is an *abnormal increase in the number or size of the capillaries and veins.*

Such formations occur most frequently in the skin and subcutaneous tissue. They are usually congenital, but increase in size after birth. They are designated **vascular nævi,** and are often found in places where fetal clefts have closed (*fissural angiomata*). In many instances it is scarcely permissible to speak of them as tumors, since the skin may show no tumor-like elevation. Teleangiectases of the skin and subcutaneous tissue, presenting either as circumscribed growths or as flat, occasionally nodular thickenings, may with propriety be termed tumors. The smooth *nævus vasculosus,* on the other hand, appears as a superficial substitution of the skin by another tissue. The color of the affected skin is *bright red*
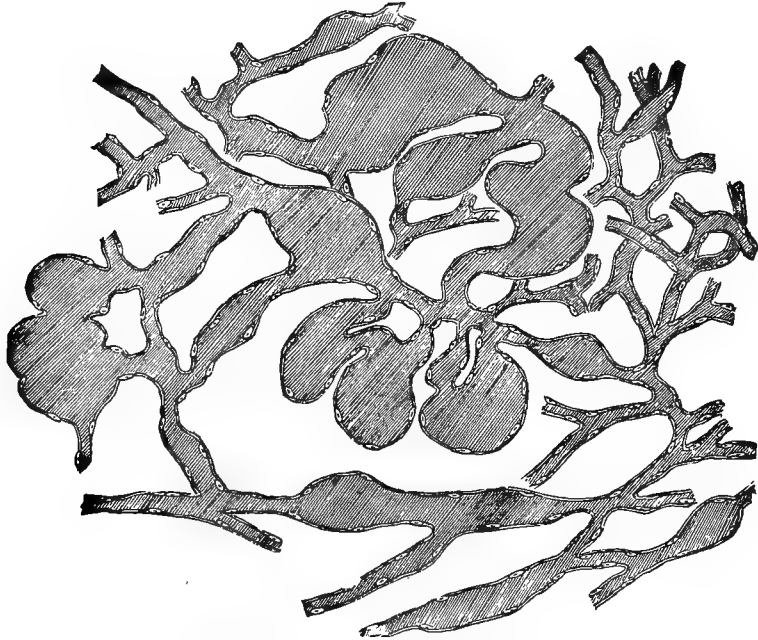
Fig. 235.—Dilated capillaries of a teleangiectatic tumor of the brain, isolated from a portion of tumor by means of shaking.   × 200.

(*nævus flammeus*) or *bluish-red* (*nævus vinosus*). The line of demarcation between normal and affected skin usually is not a sharp one; around the edge and in the neighborhood of the area of discoloration there are often found circumscribed red spots appearing as outrunners of the process.

The red color is due to dilated blood-vessels in the corium or in the subcutaneous fat tissue (Fig. 234, *a*) ; and cases occur in which large areas of subcutaneous adipose tissue present a red appearance as a result of the pathological development of blood-vessels. More rarely than in the skin and subcutaneous tissues, there occur similar angiomata in other places: in glands (mamma), bones, brain (Fig. 235), and spinal cord and their membranes. Not infrequently, on the other hand, there are found analogous vascular changes in tumors, for example, in gliomata or sarcomata.

If the vessels, which are usually abundant, are isolated, it becomes evident that the capillaries and small veins (*angioma simplex venosum*),

are more or less dilated. The dilatations (Fig. 235) are spindle-shaped or cylindrical, saccular or spherical, and different forms of dilatation may be combined in a variety of ways. The dilated vessels are united by capillaries of normal size or of moderately increased calibre. The walls of the vessels are thin — in comparison with normal capillaries they are slightly thickened.

Fig. 236.— Angioma cavernosum cutaneum congenitum (Müller's fluid, hæmatoxylin). *a*, Epidermis; *b*, corium; *c*, cavernous blood-spaces. × 20.

Hæmangioma cavernosum is a *vascular formation consisting of spongy tissue*, whose structure suggests that of the corpus cavernosum or spongiosum of the penis (Figs. 236, and 237). Through filling of the spaces with blood they present a bluish-red or dark red color.

The cavernous angioma, like the angioma simplex, occurs chiefly in the skin (Fig. 236, *c*) and subcutaneous tissues. At times it forms a small bluish-red spot; at other times, a smooth, elevated (Fig. 236), or slightly

Fig. 237.— Angioma cavernosum hepatis (Müller's fluid, hæmatoxylin, eosin). *a*, Liver tissue; *b*, angioma. × 100.

nodular bluish-red wart (*verruca vasculosa*). Extensive development of cavernous tissue in the subcutaneous or intermuscular connective tissue may produce *large tumors or elephantiasis-like disfigurations of portions of the body (elephantiasis hæmangiomatosa)*.

Within the body the cavernous angioma is found most commonly in the liver (Fig. 237, *a*, *b*), but may develop in other organs; kidney, spleen,

20

intestine, bladder, bones, muscles, uterus, brain, etc. In the liver it
appears in the form of sharply defined, dark-red areas, varying in size
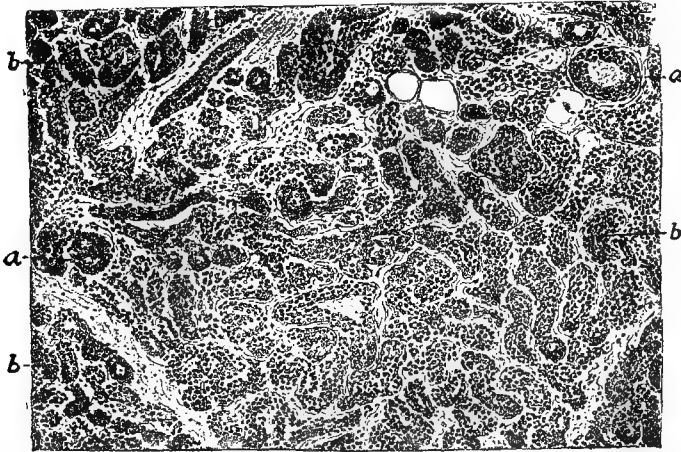
FIG. 238.—Angioma simplex hypertrophicum (formalin, hæmatoxylin). *a*, Vessels containing
blood; *b*, empty and collapsed thick-walled blood-vessels rich in nuclei. × 100.

from that of a pin-head to several centimetres in diameter. They replace
the liver tissue, and are usually flush with the surface.

The width of the blood spaces and the thickness of the limiting trabe-
culæ vary in different cases; the angioma may be rich in fibrous tissue
that was formed in the beginning, or
fibrous proliferations take place as
sequelæ to thrombosis. The blood
spaces are lined with endothelium; at
times smooth muscle-fibres may be
demonstrated in their walls, and the
interstitial tissue is often rich in elastic
fibres (Brüchanow). Usually no liver
cells are found in the trabeculæ.

The cavernous angioma of the liver
occurs in old individuals, as well as in
infants and children, and not infre-
quently is multiple. It is probably a
local disturbance of development,
which proceeds from the vessels of
Glisson's capsule or from the intra-
acinous capillaries, characterized by ab-
normal multiplication of blood-vessels
at the expense of other tissues. De-
velopment is slow and limited; ordi-

FIG. 239.—Angioma simplex hypertro-
phicum cutaneum et subcutaneum (alcohol,
carmine). In the middle of the section is
the duct of a sweat-gland cut transversely.
× 200.

narily the liver-cells in the immediate neighborhood show no signs of
degeneration.

In the majority of cases hepatic angiomata are encountered as acci-
dental findings at autopsy, and are solitary and small in size. In rare
instances, however, they attain large dimensions or occur in such numbers
as to replace no inconsiderable part of the liver substance. Occasionally

thrombosis may take place in them, subsequent organization resulting in partial or complete replacement by fibrous tissue. As a rule, hepatic
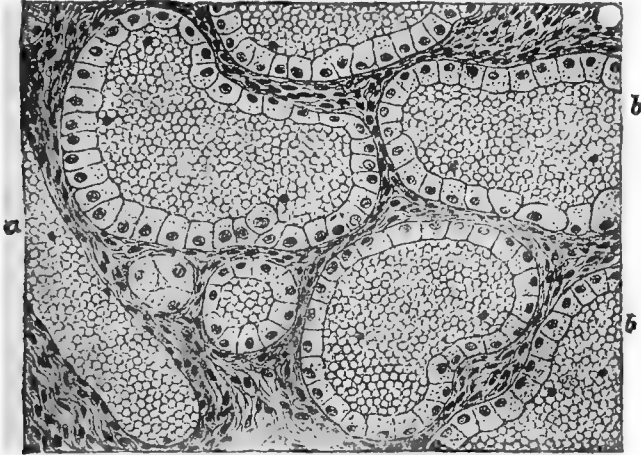
FIG. 240.—Angioma cavernosum hypertrophicum (angioendothelioma) of the skull-cap (Müller's fluid, hæmatoxylin). *a*, Blood-vessel with flattened endothelium; *b*, blood-vessel with cubical and cylindrical endothelium. × 250.
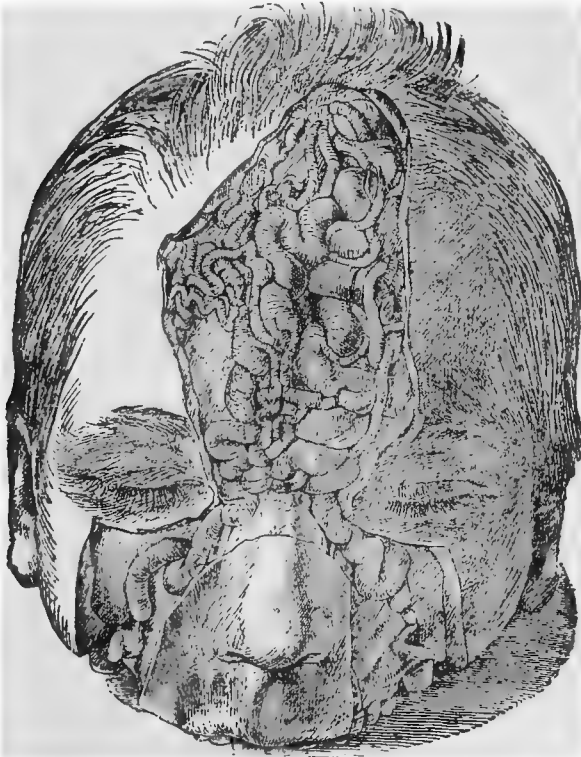
FIG. 241.—Angioma arteriale plexiforme arteriae angularis et frontalis dext. et sin.

angiomata are of no clinical significance whatever, although in a case investigated post-mortem at Bellevue Hospital, death occurred from rup-
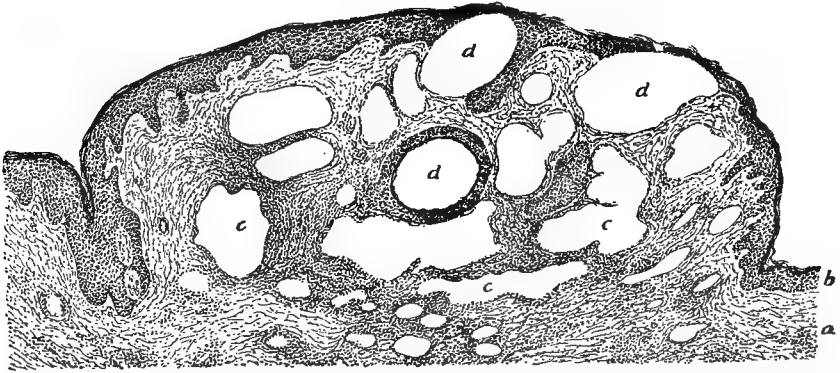
FIG. 242.— Weeping subepithelial lymphangioma of the skin (alcohol, carmine). *a*, Corium; *b*, epithelium *c*, *d*, lymph-spaces. × 14.

ture of a small angioma of the under surface of the liver with the production of massive hæmorrhage into the abdomen.

Hæmangioma hypertrophicum occurs most frequently in the skin and subcutaneous tissues, where it forms circumscribed nodules.   The altered
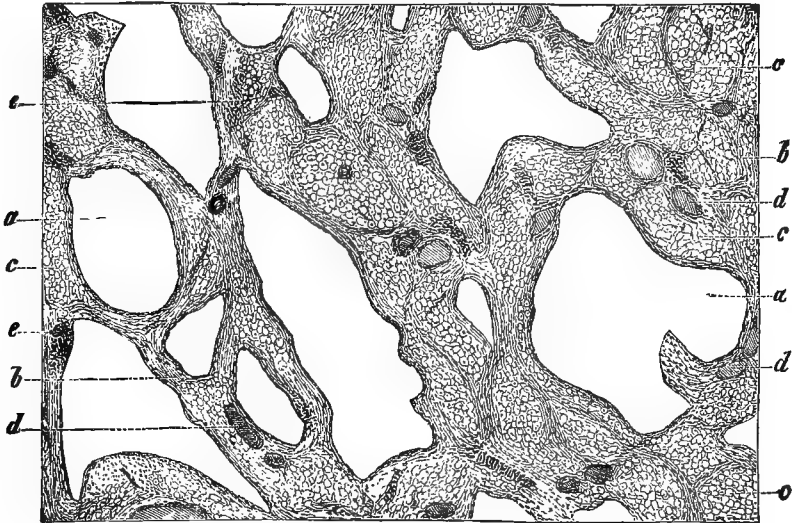
FIG. 243.— Lymphangioma cavernosum subcutaneum (alcohol, alum-carmine). *a*. Ectatic lymph-vessels; *b*, connective tissue; *c*, adipose tissue; *d*, large blood-vessels; *e*, cellular areas. × 200.

vessels lie in the papillæ and corium as well as in the subcutaneous tissue, and form tubes filled with blood (Figs. 238, *a*, and 239), the walls of which are thickened and cellular, or solid cords of cells (Fig. 238, *b*), which are either collapsed, thick-walled vessels, or possess no lumen whatever.

In very rare cases it happens that in angiomata, which from the calibre of the vessels bear the character of cavernous angiomata, there occurs hypertrophy of the vessel-walls; and this hypertrophy is due to the fact that the flat endothelial cells become changed into cubical and cylindrical cells (Fig. 240, *b*). Such a tumor may be classed as an *angioma caverno-sum hypertrophicum,* or as a *blood-vessel-endothelioma,* or *hæmangioitic endothelioma;* the last term being in particular applicable when, as a result of the marked proliferation and multiplication of the endothelium, there are produced nests of large cells which fill the blood-vessels (compare Endothelioma, §§ 114 and 115).

A cirsoid aneurism, or angioma arteriale racemosum, or angioma arteriale plexiforme (Fig. 241), is a condition in which the arteries of an entire vascular area are *dilated, tortuous,* and *thickened,* so that there is formed a convolution of enlarged and thickened arteries. To the palpating finger they feel like a bunch of earth-worms. Many of these angiomata, which occur particularly on the head, and which may cause erosion of the cranial bones, arise from congenital defects; others appear to be acquired, and develop after traumatism, but it is possible that special conditions may have existed before the trauma.

§ 108. Angioma lymphaticum or lymphangioma is a tumor the greater part of which is made up of *dilated lymph-vessels.* The following forms may be distinguished: *lymphangioma simplex* or *teleangiectasia lymphatica* (Fig. 242); *lymphangioma cavernosum* (Fig. 243); *lymphangioma cystoides;* and *lymphan-gioma hypertrophicum.* The cavities of these tumors usually enclose a clear, light-colored lymph; more rarely it is milky and

FIG. 244.— Large hairy and pigmented nævus of back, buttocks, and thighs with scattered smaller pigmented spots over the remaining portions of the body. (After Röhring.) (Reduced from original.)

contains lymphocytes. The walls consist of connective-tissue trabeculæ of varying thickness and containing more or less involuntary muscle; the spaces are lined with endothelium.

In **lymphangioma simplex** (Fig. 242) the lymph-vessels of a more or less extensive area are dilated and their walls for the greater part are thickened. In **cavernous lymphangiomata** the number of lymph-vessels is still greater, their spaces are larger, and the intervening tissue is less abundant, so that, even to the naked eye, the growth presents a spongy appearance. The **cystoid lymphangiomata** contain cysts varying in size from that of a pea to a walnut. The tissue between the dilated lymph-vessels consists, according to the location of the tumor, of connective tissue (Fig. 242), fat (Fig. 243, *c*), muscle, or lymphadenoid tissue may be enclosed (*e*), and may present evidences of active proliferation.

Lymphangiomata are sometimes congenital; at other times they appear at a later period of life.

The congenital forms occur as ectasias of lymph-vessels, and are found in the tongue (*macroglossia*), palatal arch, lips (*macrocheilia*), skin (*nævus lymphaticus*), subcutaneous tissue, in the neck (*hygroma colli congenitum*), vulva, etc. The *lymphangiomata of the skin* spread over more or less extensive areas, and form either smooth or irregular elevations. If the blood-vessels are numerous the growth may have a red color. The rupture of dilated lymph-vessels lying immediately beneath the epithelium (Fig. 242, *d*) may give rise to lymphorrhœa. The extension of cavernous lymph-vessels over large areas of the skin and subcutaneous tissue gives rise to
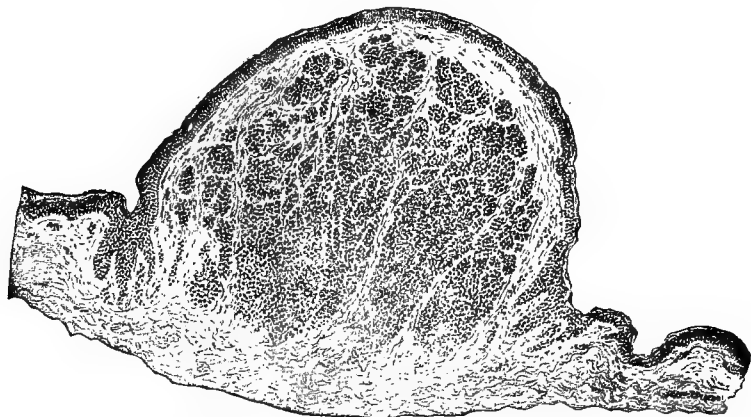
Fig. 245.— Lymphangioma hypertrophicum. Section through a small, soft, smooth wart (formalin, hæmatoxylin, eosin). × 40.

elephantiasis-like disfigurations of the part affected. Not infrequently the intervening connective tissue takes part in the hypertrophic growth.

In rare cases chyle-containing growths (*chylangiomata*) are found in the intestinal wall or mesentery. *Cystic lymphangiomata* are occasionally found in the *peritoneum*.

Hypertrophic lymphangiomata represent peculiar changes of the skin, which are either congenital or develop in early youth. Included in this general group are pigmented moles, lentigines, freckles, and fleshy warts.

The *pigmented moles, nævi pigmentosi,* or benign *melanomata,* form large or small smooth areas which are not elevated above the surface of the skin (*nævus spilus*), or prominent warty growths (*nævus prominens, nævus verrucosus*). When covered with hair, as frequently is the case, they are called *hairy moles (nævus pilosus)*. They are usually light brown or dark brown, or even black (Fig. 244); and are usually covered by epidermis of normal thickness, rarely by hypertrophic epithelium. They are usually small, but may be as large as the palm of the hand, or may even cover a large part of the body surface.

Lentigines appear at any time after birth, and on any part of the body surface; when once formed they remain for life. They form sharply circumscribed yellow to brownish-black spots closely resembling the little pigmented nævi; and vary in size from a pinhead to that of a lentil.

Freckles or *ephelides* are small, irregularly outlined, serrated, pale-brown spots, which are not elevated above the surface of the skin. They

occur in young individuals, particularly on the face, hands, and arms, rarely on other portions of the body; and may remain permanently or disappear after a longer or shorter time. The pigmentation is favored by exposure to sunlight.

Fleshy moles (*verrucæ carneæ*) are non-pigmented, circumscribed, smooth (Fig. 245) or slightly irregular, or rough and papillary (Fig. 247) prominences, over which the epidermis is at times normal, at other times somewhat hypertrophic (Fig. 247, *a*).

In all the pathological formations just described the connective-tissue framework encloses *collections of cells,* either in round or cord-like masses
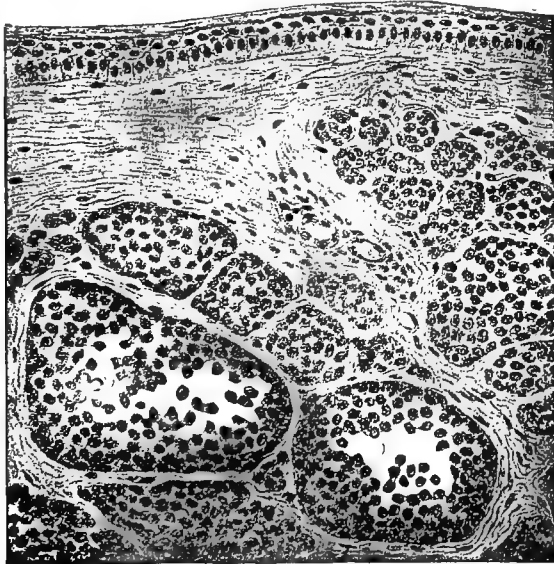
FIG. 246.—Lymphangioma hypertrophicum. Rounded summit of a large, soft, smooth wart (formalin, hæmatoxylin, eosin). Sharply outlined cell-nest in corium. × 250.

(Figs. 245, 246, 247, *d*, *d₁*), which lie partly in the papillæ and partly in the corium; and are the more abundant the more the growth projects above the surface. In the pigmented varieties the cells of the cell-nests may contain pigment in the form of brown or yellow granules, or the pigment may lie in or between the connective tissue cells of the fibrous portions of the growth.

The cells of the nests are relatively large (Fig. 246), possess abundant protoplasm, and a bright, bladder-like nucleus. Their position and appearance justify the assumption that they represent *proliferation of the endothelial cells of the lymph-vessels.* In rarer cases similar formations arise from blood-vessels (hæmangioma hypertrophicum). Accordingly, it would seem proper to class these growths with the endotheliomata, but their limited growth makes their classification as lymphangiomata more appropriate (see § 114). The cell-nests of hypertrophic lymphangioma may spread more diffusely through the tissues (as is the case with the hypertrophic hæmangioma), so that the peculiar structure of the growth may be lost.

Unna, Kromayer, Delbanco, and *Marchand* hold that the cell-nests of nævi are of epithelial origin, and represent misplaced portions of surface epithelium; *Kromayer* goes so far as to assume metaplasia of epithelium into connective tissue. Preparations showing the first stages of the development of nævi are not accessible to me; but a thorough study of nævi and fleshy warts of a later stage does not show any connection between the cell-nests and epithelium; and consequently I hold—
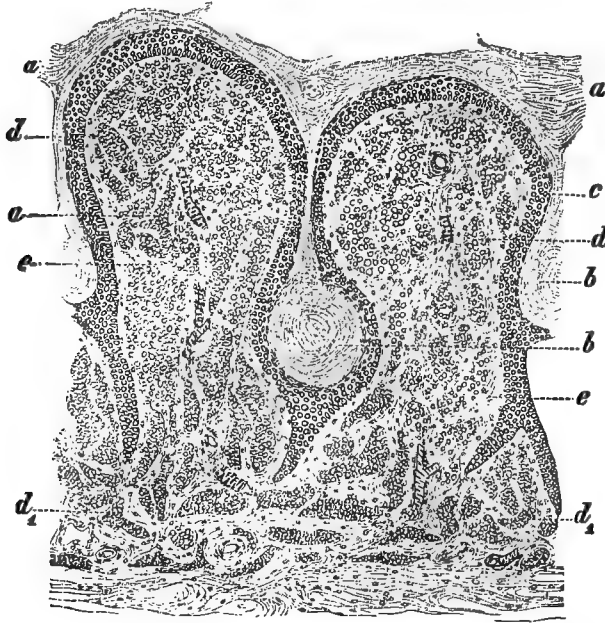
FIG. 247.— Section through two papillæ of a papillary fleshy wart (alcohol, carmine). *a*, Thickened horny layer of the epidermis; *b*, epithelial pearls; *c*, rete Malpighii; *d*, nests and strands of cells in the papillæ; *d₁*, nests and strands of cells in the reticular layer; *e*, connective tissue. × 50.

notwithstanding the investigations of others — that the view given above harmonizes with the anatomical nature and clinical behavior of these growths, both in their fully developed condition as well as when they undergo malignant transformation. That the cell-nests lie close to the epithelium is no proof of genetic relationship, since the ordinary lymphangiomata also lie close to the epithelium (Fig. *d*). According to investigations by *Jadassohn* and *Lanz* the cellular warts can be transplanted from one individual to another by an intra-epidermoidal inoculation of cell-masses.

(g) Myoma.

§ 109. A **myoma** is a tumor consisting of *newly formed muscle-fibres.* According to the nature of the muscular elements, myomata are divided into *leiomyomata* formed of *unstriped muscle,* and *rhabdomyomata* composed of *striped muscle.*

The **leiomyoma,** or *myoma lævicellulare,* occurs frequently in the uterus, more rarely in the tubes, uterine ligaments, labia majora, muscularis of the gastro-intestinal tract and urinary passages; and may form spherical, nodular tumors of varying size. In rare cases it is also found in the skin and subcutaneous tissues, forming nodules occasionally reaching the size of a pigeon's egg. Leiomyomata occur as single or multiple

tumors; and may appear in childhood, or even during intrauterine life (Marc).

In muscular organs the new-growth proceeds from the muscularis, and forms bundles of muscle-fibres (Fig. 248) which are interwoven in such fashion as to present a variety of pictures according to the direction in which the bundles are cut. Myomata of the uterus may contain uterine glands, and those developing in the dorsal wall near the angles of the tubes, or in the inguinal region, may include gland-tubules from the Wolffian body (von Recklinghausen); such tumors may be designated
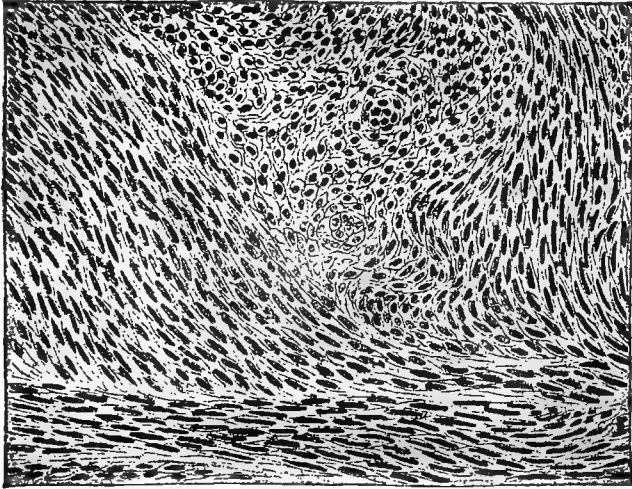
FIG. 248.— Myoma of the uterus (Müller's fluid, hæmatoxylin, eosin). × 300.

adenomyomata. They are distinguished from ordinary myomata, which are circumscribed, by the fact that their boundaries are not sharply defined. Eventually some of the glands may become cystic from accumulation of secretions. According to Ricker, Pfannenstiel, and others, uterine myomata as well as those of the vaginal vault may contain epithelial tubes, which probably owe their origin to inclusions of portions of the duct of Müller. In the skin and subcutaneous tissue the formation of muscle-fibres proceeds from the muscularis of the vessels (Fig. 249), which become thickened (*a*), and give rise to free strands of muscle-fibres (*b*). Pathological new-formation of blood-vessels may be associated with that of muscle (*a*), so that tumors arise which are designated *angiomyomata* (Fig. 249). According to Jadassohn and others, multiple myomata of the skin may take their origin from the arrectores pilorum or from the muscle-cells of sweat-glands.

A certain amount of connective tissue always takes part in the formation of a myoma, and often assumes such importance that the tumor is called **fibromyoma** or **myofibroma**. The majority of uterine myomata are fibromyomata. The fibrous portions of the tumor appear glistening white, the muscular portions reddish-white or reddish-gray. The spindle-shaped muscle-fibres may be isolated by teasing a bit of the tumor or by maceration in nitric-acid solution or potassium hydroxide. In longitudinal sections the muscle-fibres are recognized by their rod-shaped nuclei (Figs. 248, 249), as well as by the arrangement of the cells in bands or strands.

In cross-section the muscle-cells appear as small flattened cells containing in their centres the transversely cut nuclei (Fig. 248).

The leiomyomata are benign tumors, but often reach large size, and sometimes undergo sarcomatous transformation and set up metastases. The muscle-cells themselves may multiply or the intermuscular connective tissue take on sarcomatous proliferation. In fibromyomata of the uterus fatty degeneration may lead to softening or to the formation of cystic
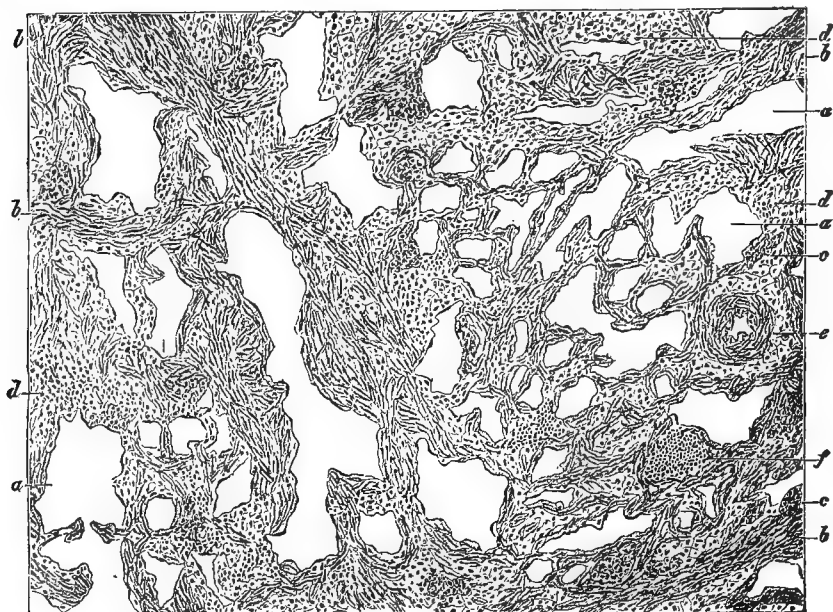
FIG. 249.—Angiomyoma subcutaneum dorsi (alcohol, hæmatoxylin, eosin). *a,* Cavernous blood-vessels; *b,* strands of muscle cut longitudinally; *c,* same cut transversely; *d,* connective tissue; *e,* artery with hypertrophic muscularis; *f,* groups of lymphoid cells. × 46.

cavities. Calcification and bone-formation may also occur. Through degeneration and atrophy of the muscle-fibres a myofibroma may become transformed into a fibroma.

By far the greater number of tumors composed of smooth muscle tissue originate in the uterus, and it is estimated that between 1 and 2 per cent. eventually undergo malignant transformation (Kelly and Cullen). This may be brought about in one of two ways: first, by the development of genuine sarcomata from the connective tissue of the interstitium, and, second, by direct transformation of the muscle fibres, or mesodermal elements, into cells whose histology and vegetative vagaries correspond to the form and behavior of the cells of an autonomous malignant growth. Strictly speaking, this latter type of tumor should not be classified among the sarcomata, but as a malignant myoma. For practical purposes, however, most writers on the subject employ the term myosarcoma to designate a malignant tumor which develops either from the connective tissue framework or from the smooth muscle elements of a leiomyoma. In still other quarters it is maintained that the proliferation of muscle cells occurs primarily in the walls of the blood-vessels with which the tumor is provided.

In addition to the familiar uterine leiomyomata, smaller but histologically identical tumors occasionally are to be observed at autopsy or operation, either singly or in numbers, lying in the musculature of the stomach, intestine, gall-bladder and elsewhere. In the autopsy experience at Bellevue Hospital they occur in less than 1 per cent. of cases and the individual tumors rarely exceed a centimetre in diameter, projecting, as a rule, beneath the serous surface, sometimes into the lumen. They are apt to be regarded as interesting but otherwise negligible. As a matter of fact, there is evidence to show that these apparently insignificant growths undergo malignant transformation with a degree of frequency which entitles them to notice as factors of clinical importance.

Rhabdomyoma, or *myoma striocellulare,* is a rare tumor composed of striated muscle-fibres, which in part are fully developed and in part undeveloped. When well developed the muscle-fibres form multinuclear bands of varying width, which present cross-
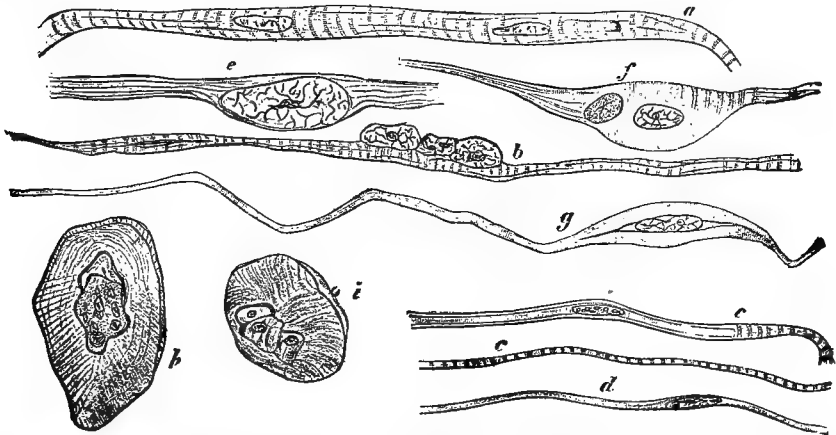
FIG. 250.—Cells from a rhabdomyoma. (After Ribbert and Wolfensberger.) *a, b, c, c,* Striated fibres of varying thickness; *d,* slender nucleated fibre without striation; *e,* spindle-cell with longitudinal striation; *f,* spindle-cells with longitudinal and transverse striation; *g,* spindle-cells, without striation, with elongated processes; *h, i,* round cells with concentric and radial striation.

striation (Fig. 250, *a, b, c*), and also longitudinal striation (*e, f*). The undeveloped forms consist of narrow bands without transverse striations (*d*); spindle-cells with long-drawn-out thread-like processes without transverse striation (*g*) or with partial striation (*f*); or round cells of different sizes, which present either radial or concentric fibrillation or striation (*h, i*). Besides these there are cells which possess no special characteristics, so that it is impossible to determine whether they are young muscle or connective-tissue cells. The bands as well as the spindles are usually arranged in interlacing bundles. It is not possible definitely to demonstrate sarcolemma on the surface of the fibres; but various delicate membranes have been described which probably are to be regarded as a rudimentary sarcolemma.

Rhabdomyomata of the heart are peculiarly constructed in so far as they do not consist of transversely striated muscle-fibres, but are made up of a network in which lie spider-like cells, whose processes are partly free, and partly continuous with the connective tissue reticulum. According to

Seiffert, these are to be regarded as enlarged embryonal muscle-cells, which have formed no transversely striated covering.

Rhabdomyomata occur in the kidney, testicles, uterus, vagina, bladder, heart, subcutaneous tissue, œsophagus, etc., and form nodular, or, if on a mucous membrane, papillomatous and polypoid tumors. They develop from striped muscle, possibly from smooth muscle (uterus).

If a tumor contains only a few cells which can be definitely recognized as muscle-fibres, while the majority of the cells have no specific character, the tumor is ordinarily designated *rhabdomyosarcoma*.

(h) *Glioma and Neuroglioma Ganglionare.*

§ 110. A **glioma** is a tumor which develops from the *cells of the supporting tissue of the central nervous system* (neuroglia). In the brain gliomata form tumors which are not sharply defined from normal brain-substance, but pass into the latter by insensible gradations. At times they appear as local swellings of the brain, and only the difference in color and consistence and the disappearance of contrasts between the different elements of the brain, give evidence that a tumor is present. In the spinal cord they arise most frequently in the neighborhood of the central canal, and may extend over a large portion of the cord.

Their appearance varies greatly; sometimes they are light-gray, somewhat translucent, and similar in color to that of the cortex, and moderately firm in consistence; at other times they are grayish-white, dense, and firm; again they are not infrequently grayish-red or dark red and sharply circumscribed from the surrounding brain, and traversed by numerous large vessels. Gliomata well supplied with blood

FIG. 251.— Glioma cerebri. *A,* Cells isolated by teasing and stained with carmine. *B,* Section from same glioma after hardening in Müller's fluid (Bismarck brown). × 350.

often contain hæmorrhagic areas. Fatty degeneration, softening, and destruction of the tissue are of common occurrence.

A fully developed glioma shows under the microscope a network of delicate fibrillæ (Fig. 251, *B*), in which are imbedded numerous short oval nuclei. About the nuclei there is scanty protoplasm, to be distinguished only with difficulty. When examined in the fresh state or after maceration it may be seen that these nuclei belong to cells (astrocytes) which are characterized by fine processes extending in all directions, and often branching (Fig. 251, *A*). By proper staining the connection between some of the fibres may be demonstrated (Fig. 252).

The cells are similar to normal glia-cells; but are frequently larger, occasionally more plump, and may possess two, three, or four nuclei. A preponderance of cells with slight development of processes leads to

the formation of *medullary gliomata;* more marked formation of processes and of fibrillated ground-substance gives rise to *hard forms.* As the result of proliferation of the perivascular connective tissue *gliosarcomata* may be formed.

In gliomata developing in the neighborhood of the ependyma, the *ependymal epithelium may share in the proliferation,* and the surface of the tumor becomes covered with a layer of ependyma. *Epithelial ingrowths resembling ducts* may be formed, so that the tumor *takes on the character of an adenoma (neuro-epithelioma adenomatosum gliomatosum).*

A similar appearance may be produced when misplaced portions of the medullary canal lie in the glioma.

Proliferations arising from the epithelium of the choroid plexus bear the character of epithelial growths.

Neuroglioma ganglionare (Fig. 253) ·is a *tumor of the central nervous system,* composed of hyperplastic *glia-tissue, ganglion-cells,* and *nerve-fibres,* and forms poorly defined swellings of large portions of the brain, or circumscribed, nodular enlargements of smaller portions. To the naked eye the structure of the brain may appear to be preserved, though the difference between cortical

FIG. 252.— Section of a glioma of the cerebrum, with astrocytes (Müller's fluid, hæmatoxylin, Mallory's method.) × 500.

and medullary substance is less distinct than normal, and the tissue throughout is white or grayish-white, or spotted gray and white, and more or less increased in consistence.

The main portions of these masses consist of glia-tissue containing nerve-fibres (d) and ganglion-cells (a, b, c), or cells resembling ganglion-cells, not only in the cortical tissue, but in the white substance.

Probably all of these formations are to be regarded as the result of disturbances of development — that is, as local malformations characterized by *pathological development of neuroglia (gliomatosis)* and by development of neuroblasts, probably also of spongioblasts, into *ganglion-like cells (a)* such as are not normally found in the brain.

The term **glioma** is also applied to certain tumors of the **retina** occurring during childhood. These growths are evidently to be referred to disturbance in the development of the retina. They form cellular, soft, white or reddish tumors, the greater part of which consists of small, round or irregular cells poor in protoplasm, resembling the cells of the stratum granulosum. Some of them possess smaller or larger processes. These cells are best preserved in the neighborhood of the blood-vessels; in other portions of the tumor they often show retrograde changes. The tumor may also contain ganglion-cells, cylindrical cells, and rosette and ribbon-like cell-formations, regarded as aggregations of rods and cones. Wintersteiner has designated the tumor *neuroepithelioma.*

The glioma of the retina often shows areas of necrosis in its central portion. In its growth it may break into the retrobulbar space, or forward through the cornea and sclera; it recurs after operation, and gives rise to metastases.

The **neuroblastoma** is a malignant tumor composed of undifferentiated nerve cells or neuroblasts, and arises most often in the medulla of the suprarenal capsule, but occasionally in other parts of the body. Histologically, the tumor is characterized by the presence of rosettes made up peripherally of cells with richly chromatic, rounded nuclei, surrounding tangled masses of fibrillated or homogeneous material staining pinkish with eosin, the latter representing the remains of cell fibrils. In certain cases the fibrils are absent or poorly developed, rosettes cannot be seen, and the richly nucleated character of the growth in these circumstances may lead to the diagnosis of sarcoma. The condition is not common. It occurs oftenest in children, in whom there are two symptomatic groups; one attended by an abdominal mass with secondary exophthalmus, ecchymosis of the lids, infiltration of the bones of the skull and of the regional lymph nodes; the other by rapidly increasing distention of the abdomen due to neoplasmic infiltration
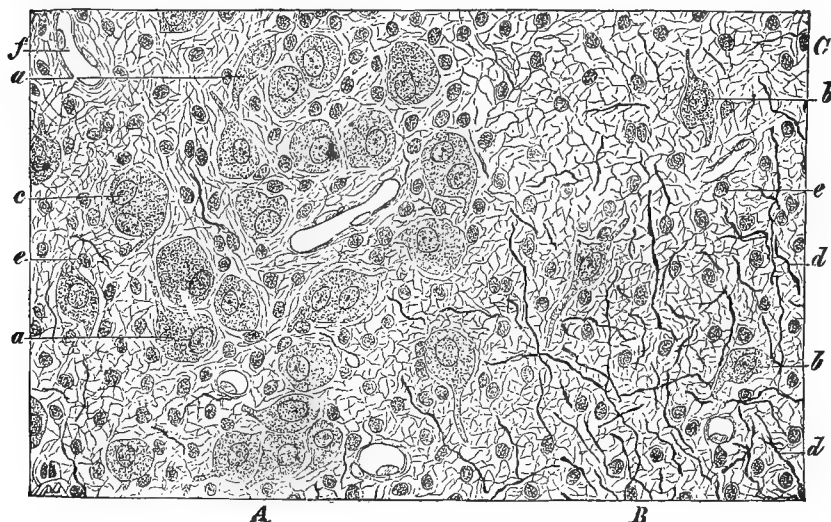
FIG. 253.— Section from a nodular neuroglioma ganglionare of the central convolution of the cerebrum (Müller's fluid, Weigert's stain). *A*, Portion of tissue rich in ganglion cells. *B*, Portion of tissue containing nerve-fibres. *C*, jelly-like portion. *a*, Ganglion-cells arranged in groups; *b*, scattered ganglion-cells; *c*, ganglion-cells with two nuclei; *d*, nerve-fibres with medullary sheath; *e*, glia-cells; *f*, blood-vessel. × 275.

of the liver unattended by ascites or jaundice . (Wright, Journal Experimental Medicine, 1910; Hutchison, Quarterly Journal of Medicine, 1917; Pepper, American Journal Medical Sciences, 1901.)

With reference to the origin of neuroglia and ganglion-cells from the ectoderm, various writers class the *different forms of gliomata* with the epithelial tumors. In so far as ependymal proliferations resembling epitheliomata and adenomata (§§ 118, 119) are concerned, such a classification is justified. The ordinary gliomata, however, show a structure resembling that of the other connective-tissue tumors, so that it is more proper to class them with the latter.

(i) Amputation Neuroma, Neurofibroma, and the True Neuroma.

§ 111. The tumors designated **neuromata** occur most frequently on the ends of amputated nerves, where they form more or less prominent swellings, either circumscribed or blending into the surrounding tissue, and are familiarly known as *amputation-neuromata* (Fig. 254, *b*). The development of these neuromata is to be referred to changes taking place after the nerves have been severed; during the development of connective tissue in the stump the axis-cylinders of the proximal portion of the

nerve divide and grow longitudinally, so that the scar is penetrated by nerves which at first have no sheaths, but are soon surrounded by medullary sheaths. The number may be so large as to permeate the connective tissue in all directions (Fig. 254, *b*). The process is an example of useless *regenerative proliferation.*

Another form of so-called neuromata are those growths developing spontaneously along the course of nerves; and consist of *increase in the connective tissue of the nerve,* usually of the outer, more rarely of the inner layer of the endoneurium.

At the point of tumor-growth the nerve-bundles become surrounded by a more or less thick layer of connective tissue, which is usually loose, more rarely dense (Fig. 255, *b, d*), or the bundles may be split into individual fibres (*c*). Occasionally the perineurium takes part in the proliferation. In large nerve-trunks the epineurium may be affected in association with the endo-neurium and perineurium of individual bundles, although the process is most frequently confined to the endoneurium.

These tumors are not true neuromata, but **neurofibromata** or **fibromata nervorum.** They are usually *multiple,* and may extend through the entire peripheral nervous system, but are more often limited to a definite area of nerve-distribution. In rare cases they occur in the nerve-roots and spinal cord. The nodules are sometimes situated along the course of the nerve-trunks, sometimes on the finer branches, most frequently of the cutaneous nerves; and in the skin form numerous, large or small nodules, for the greater part of soft consistence, to which the designation **multiple fibromata of the skin** is applied. The smallest nodules can be seen only with the microscope; the majority vary in size from a pea to that of a hazel-nut. Individual tumors may reach the size of a man's fist, the nerve-fibres being lost in the mass of connective tissue. Atrophy of the fibres may be caused by the increasing connective tissue, the fibres finally vanishing. In addition to the formation of circumscribed nodules there may occur *diffuse thickening of the nerves from hypertrophy of their connective tissue.* Moreover, there may be associated hypertrophic proliferation of the connective tissue of the skin and subcutaneous tissue, leading to *elephantiasis-like thickenings.*
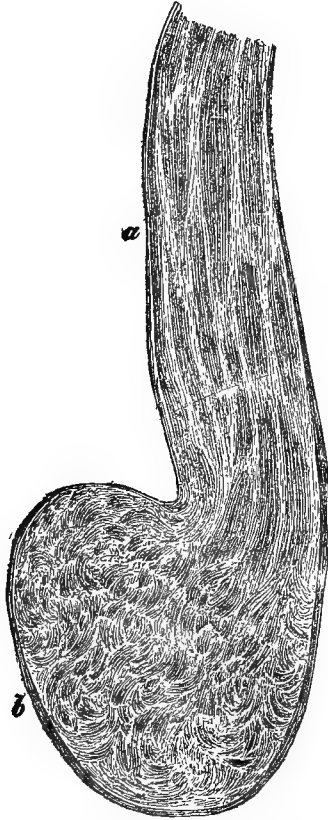
FIG. 254.—Amputation-neuroma of the sciatic nerve (nine years after amputation of the nerve). Longitudinal section. *a*, Nerve; *b*, neuroma; drawn from a preparation which had been hardened in Müller's fluid. × 3.

A third form of false neuroma is the **cirsoid** or **plexiform neuroma,** which is characterized by the development in the domain of one or more nerve-branches of tendril-like, twisted or interwoven, thickened and

nodular nerve-strands (Fig. 256). When examined in detail this forma-
tion is also found to depend on *fibromatosis of the nerves* (Fig. 255), the
proliferation of the endoneurium resulting partly in diffuse and partly
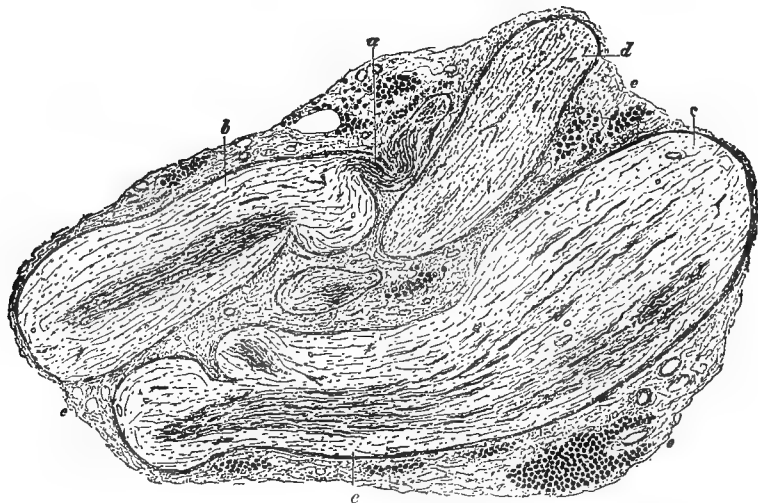
FIG. 255.— Nerves from an elephantiasis-like cirsoid neuroma of the cheek and lower jaw (Flemming's solution, safranin). *a, b*, Nerves, the outer layers of whose endoneurium have undergone marked proliferation; the nerve-fibres lie in the axial portion; *c*, nerve with markedly proliferated endoneurium and separated nerve-fibres; *d*, thickened nerve with a small strand of nerve-fibres at the left end; *e*, loose connective tissue, rich in nuclei and containing fat, lying between the nerves. × 7.
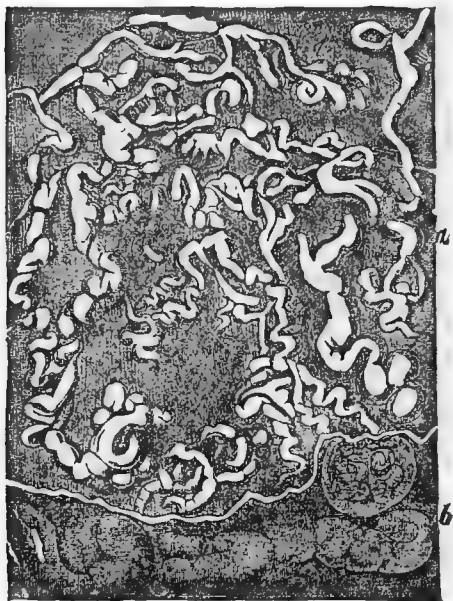
FIG. 256.— Cirsoid neuroma of the sacral region. (After a drawing by P. Bruns.) The nodular, twisted, and interwoven nerves are in part free (*a*), and in part (*b*) covered by connective tissue. Natural size.

in nodular thickening. In addition, it may be found that the nerves of the affected area are *lengthened and tortuous,* and at the same time *increased in number.* In these circumstances the condition must be regarded as one of true neuroma, or *neuroma* associated with *fibromatosis.* The nerves for the greater part are medullated (*neuroma myelinicum*). It is difficult to determine to what extent non-medullated nerves are present in such formations, but cases have been reported in which the nerve-fibres were largely of the non-medullated variety (*neuroma amyelinicum*). Cirsoid neuromata occur on the head, trunk, and extremities, and give rise to *elephantiasis-like disfigurations.*

True neuromata *consisting of nerve-fibres and ganglion-cells* (*neuroma gangliocellulare verum*) are rare; but the occurrence of such growths cannot be doubted. They form tumors varying in size from a millet-seed to that of an apple, and consist of connective tissue, non-medullated and medullated nerve-fibres, and ganglion-cells which resemble those of the sympathetic ganglia.

Neither the neurofibroma nor the true neuroma forms metastases, but cases occur in which neurofibromata take on a sarcomatous character and thus become malignant.

(k) Sarcoma.

§ 112. A **sarcoma** *is a connective-tissue tumor whose cellular elements, either because of their number or size, predominate over the intercellular substance.* Sarcomata are closely related to undeveloped connective tissue, and may be compared with *embryonal tissue.*

Sarcomata develop either in previously normal tissue belonging to the connective-tissue group — in the skin, subcutaneous or intermuscular connective tissue, periosteum, spinal cord, meninges, connective tissue of glands, etc.— or in some preëxisting connective-tissue tumor, as a fibroma, myoma, chondroma, hypertrophic lymphangioma, etc. The transformation of the parent tissue into tumor tissue takes place through the multiplication of existing cells. The division of cells takes place chiefly by mitosis, and mitoses are the more abundant the more rapid the growth of the tumor. In addition to typical mitoses there are frequently observed atypical forms, nuclear fragmentation, and, more rarely, segmentation.

Fully developed sarcomata form more or less sharply circumscribed growths. They may appear in any portion of the body where connective tissue is present; but are found in certain tissues more frequently than in others. Thus, they are found much oftener in the skin, fascia, intermuscular connective tissue, bone-marrow, periosteum, brain, and ovaries, than in the liver, intestines, and lungs.

The development and form of the cells vary greatly in different sarcomata. The intercellular substance is sometimes scanty, soft, and delicate; at other times abundant and resembling the ground-substance of mature connective-tissue.

The amount of intercellular substance has a marked influence on the consistence and color of the tumor. The **medullary forms** are soft and cellular, and poor in intercellular substance; on section they present a marrow-like white or grayish-white surface. The hard, dense forms, on the other hand, are poor in cells and rich in fibrous intercellular substance; they pass by insensible gradations into transition-forms known as **fibrosarcomata.** The cut surface of a sarcoma presents a nearly uniform appearance, provided retrograde changes or differences in the blood-content do not interfere; sometimes the vessels are numerous, large, and ectatic (*teleangiectatic sarcoma*). Usually the vessels have walls easily distinguishable from the tumor tissue; but the tumor-cells may form the vessel-wall. Retrograde changes — fatty degeneration, mucous degeneration, necrosis, hæmorrhage, gangrene, ulceration — are of frequent occurrence in sarcomata.

The sarcomata may be divided into three classes. The first includes *simple sarcomata* — tumors of the type of embryonal connective tissue, showing more or less uniform distribution of cells without the formation of distinct groups of cells. The second class includes sarcomata which

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show *special arrangement and grouping of the individual elements,* so that
growths arise which are similar to the epithelial tumors.   The third class
is characterized by *secondary changes in the cells, intercellular substance,
and blood-vessels.*

The *etiology of sarcoma* is not simple.   It occurs more frequently in
youth than in old age.   Some sarcomata develop even in embryonal life.
Occasionally trauma appears to be an exciting cause.   A parasitic origin
has not been demonstrated (see Etiology of Carcinoma).   Usually only
one primary tumor is formed, but multiple primary sarcomata sometimes
occur, particularly in the skin, bone-marrow and lymphoid depots.   The
softer tumors give rise to metastases.

§ 113. The **simple sarcomata** include medullary forms and those of
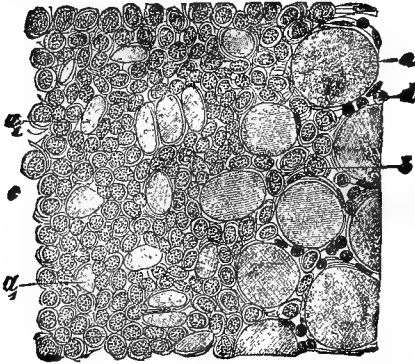
FIG. 257,   FIG. 258.

FIG. 257.— Section through the edge of a sarcoma of the intermuscular connective tissue of
the cervical muscles (alcohol, carmine). *a,* Transverse section of normal muscle; *a₁,* transverse
section of an atrophic muscle-fibre; *b,* round cells of the sarcoma, between the muscle-fibres; *c,*
fully developed tumor; *d,* lymphocytes.   × 300.
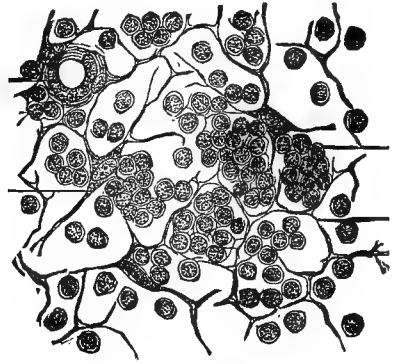
FIG. 258.—Section from a lymphosarcoma of the nasal mucous membrane (alcohol, carmine).

firmer consistence, which pass by insensible transition into *fibrosarcomata*
and *fibromata.*   According to the character of the cells, several forms may
be distinguished.

The **small round-cell sarcomata** are soft, quickly growing tumors,
which develop particularly in the connective tissue of the skeletal muscles,
and in the skin, testicles, ovaries, and lymph-nodes.   On section they
appear milky-white, and occasionally present caseous or softened areas.
When scraped the cut surface yields a milky fluid.   Their structure is
simple; the tumors consist almost wholly of round cells and blood-vessels
(Fig. 257, *c*). The cells are small, they possess little protoplasm, and have
spherical or slightly oval, rather large, bladder-shaped nuclei (*c*), which
appear to be more highly developed than the nuclei of lymphoid cells.

Between the cells lies a scanty amount of fibrogranular intercellular
substance.   The vessels traverse the growth in the form of thin-walled
canals.   If such a tumor growing in muscle be examined at its periphery
it appears as an aggregation of round cells (Fig. 257, *b, c*) in the inter-
muscular connective tissue.   Not infrequently lymphoid cells lie near
the tumor-cells, the nuclei of the former (*d*) staining more intensely than
those of the tumor-cells.

A second form of round-cell sarcoma is designated **lymphosarcoma or sarcoma lymphadenoides**; it imitates the structure of a lymph-node, in that the stroma supporting the lymphoid cells consists of a vascular
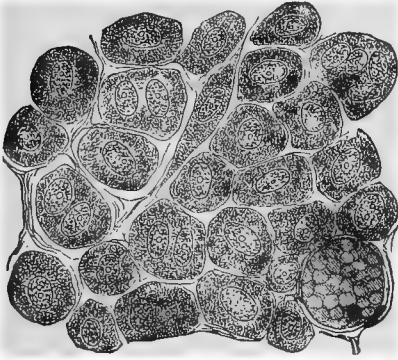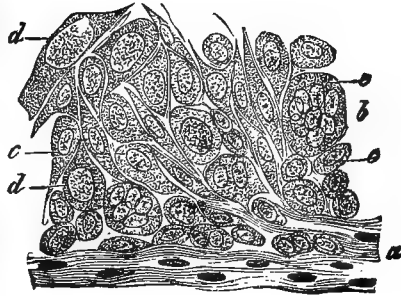
FIG. 259.— Section from a fungoid large round-cell sarcoma of the skin of the leg (carmine preparation). × 400.

FIG. 260.— Section from a sarcoma of the mamma with cells of different shapes (alcohol, Bismarck-brown). a, Connective tissue; b, sarcoma tissue; c, small cells; d, cells with hypertrophic nuclei; e, multinuclear cells. × 300.

reticulum (Fig. 258, a) composed of branching and anastomosing cells (b).

According to the amount of reticulum, the *lymphosarcomata* may be divided into *soft* and *hard* forms. In the denser varieties the reticular framework may take on the appearance of ordinary fibrous connective

FIG. 261.—(Bellevue Hospital.)   Massive spindle cell sarcoma of breast (weight 25 lbs.).

tissue. Special forms of round-cell sarcoma arising in the bone-marrow are known as **myelomata.**

Lymphosarcomata arise most frequently in the lymph-nodes and the adenoid tissue of the mucous membranes and of the spleen, but are found in other places.

Large round-cell sarcomata, the cells of which are larger than those of the forms just described, appear in the same places as do the small round-cell variety, and closely resemble the latter. The cells possess abundant protoplasm and large, bladder-like, oval nuclei (Fig. 259). Many of the cells have two nuclei, some more than two. Between the round cells there lies a reticulated substance (Fig. 259), as well as spindle-shaped and branched cells, which form a supporting alveolar network.
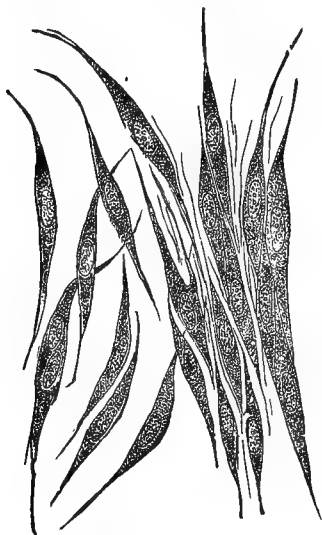
FIG. 262.

FIG. 263.

FIG. 262.— Spindle-cells from a large spindle-cell sarcoma of the cheek (teased preparation). × 400.
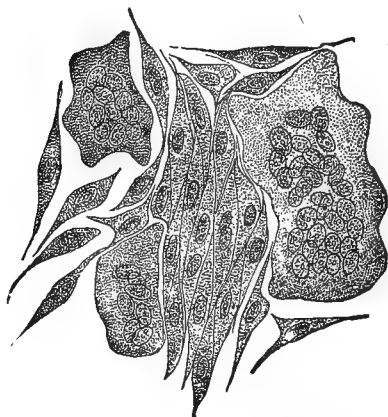
FIG. 263.— Cells from a myelogenous giant-cell sarcoma of the tibia. (Hæmatoxylin.) × 400.

In other forms of large round-cell sarcomata the tumor-cells are unequal in size (Fig. 260), and at the same time there are mingled with them elongated or irregularly shaped cells, so that the tumor may be regarded as a **sarcoma with polymorphous cells.** The nuclei likewise vary in size (Fig. 260), and (*e*) may be present in large numbers (multinuclear giant-cells).

The large round-cell sarcomata and the polymorphous-cell variety are on the whole less malignant than the small-cell, but they also give rise to metastases.

Spindle-cell sarcomata belong to the most commonly occurring tumors. As a rule, they are firmer than the round-cell varieties, but medullary forms also occur. On section they present a grayish-white or yellowish-white, translucent surface, which may be more or less reddened according to the degree of vascularity. Medullary tumors whose cells have undergone fatty degeneration may possess a pure white color. In general, these sarcomata are more benign than the round-cell varieties, but their character in this respect varies according to location and their richness in cells.

According to the size of the cells there are distinguished **large spindle-cell** and **small spindle-cell sarcomata.** The cells lie with their flat sides approximated, and are grouped in bundles, which, in section, are cut longitudinally, transversely, and obliquely — evidence that they are interwoven in different directions.

The arrangement in bundles is often striking; in other cases it is wanting; and the spindles for considerable distances run in the same direction. Sometimes the direction of the spindles is determined by that of the blood-vessels — that is, individual bundles form sheaths about the blood-vessels.

Between the spindles there is often but scanty intercellular substance, or it may not be possible to demonstrate it at all. In other cases it may
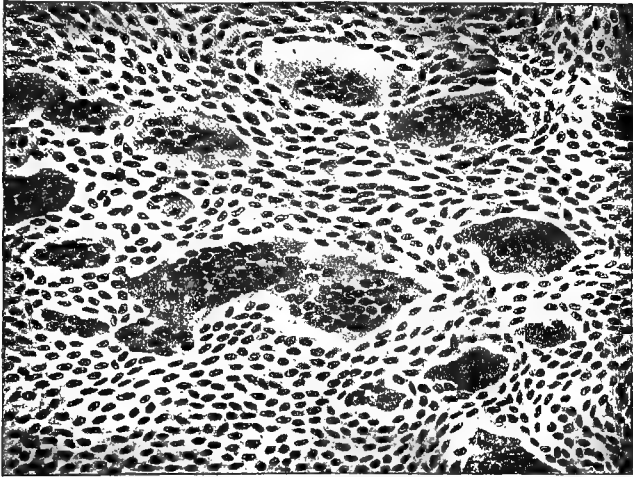
Fig. 264.— Giant-cell sarcoma of the upper jaw (Müller's fluid, hæmatoxylin). × 100.

be more abundant, and show a fibrillar character. Such varieties are dense and hard. They represent the connecting-link between sarcomata and fibromata, and are designated **fibrosarcomata.**

Sarcomata with polymorphous cells are also found among the spindle-cell forms; and contain spindle-shaped, pyramidal, prismatic, stellate, and various irregular forms (Fig. 263).

Both in polymorphous- and spindle-cell sarcomata there may be numerous giant cells (Figs. 260, 263, and 264), and the designation **giant-cell sarcoma** is applied to these tumors. They arise particularly from the bones, but may also occur in other places.

If a sarcoma develops in preëxisting new growths there may be formed mixed tumors, known as **myxosarcoma** (Fig. 222), **chondrosarcoma** (Fig. 227), **myosarcoma,** etc.

Lymphosarcoma is essentially a growth of regional distribution and anatomically may be divided into five groups, (a) *involving regional collections of superficial lymph nodes, as in the neck, axilla and groin,* (b) *implicating the lymphoid structures of the thorax,* notably the remains of the thymus gland and the lymph nodes at the root of the lung, (c) involving the *lymphoid tissues of the abdomen,* including the stomach, intestines, spleen and lymph nodes, (d) *diffuse infiltration of tissues,* especially the paired organs, and (e) *leukosarcoma,* which is characterized

by the formation of lymphoid tumors in peculiar situations, such as the uterus, breast, skin, etc., the growths pouring lymphocytes into the blood in such quantities as to constitute a form of leukemia. In the same category certain pathologists are inclined to place chronic lymphatic leukemia and its companion lesion, pseudo-leukemia. The implication of paired organs in lymphosarcoma is well shown by the lesion first fully described by *Mikulicz,* which is characterized by infiltrative overgrowth of the lymphoid cells in the stroma of the lachrymal glands, and is manifested by symmetrical enlargement of the outer two-thirds of the upper lids, followed by symmetrical invasion of the parotid and submaxillary glands. There is also a form of symmetrical conjunctival lymphosarcoma. In still another variety, lymphosarcoma brings about symmetrical neoplasmic infiltration of other paired viscera, such as the mammary gland, ovaries, testicles, suprarenal capsules and kidneys. In three cases of the latter description encountered at Bellevue Hospital, the kidneys were enormously increased in size, due to the infiltration of hordes of lymphocytes associated with lymphosarcomata in other parts of the body.
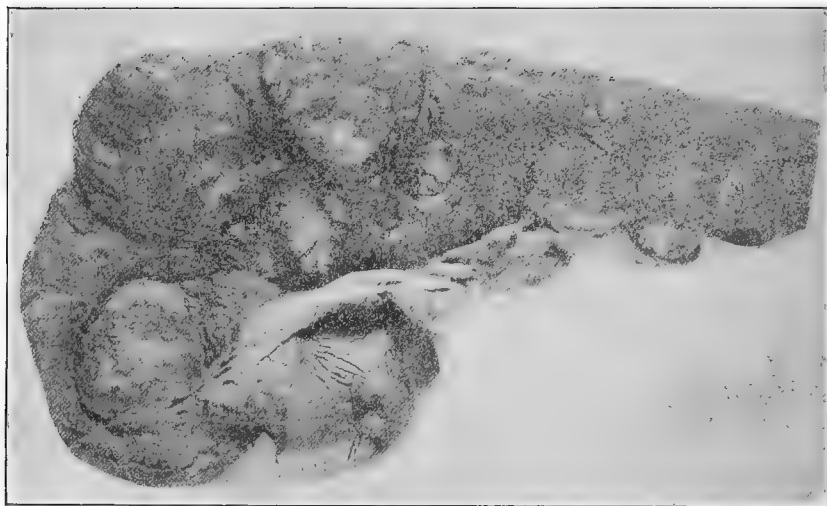
FIG. 265.—(Bellevue Hospital.) Changes in the spleen in Hodgkin's disease, the whitish areas representing nodular formations, the histology of which corresponds to that found in the lymph nodes and elsewhere.

At this point may be mentioned another peculiar process involving lymphoid tissues, namely, the so-called **Hodgkin's disease,** Clinically it often resembles lymphosarcoma, pseudo-leukemia and even true chronic lymphatic leukemia, but histologically it is distinctive. It is characterized by multiple, discrete enlargement of regional lymph nodes, notably those of the neck, axilla and groin, followed by similar changes in the lymph nodes of the thorax and abdomen. The lymphoid structures in the spleen are likewise changed and the organ becomes markedly enlarged and nodulated; the liver may be similarly riddled. Histologically the changes in the lymph nodes and elsewhere are characterized by diffuse overgrowth of connective tissue with varying degrees of hyperplasia of the lymphoid cells, together with numbers of mononuclear and multinuclear giant cells, eosinophiles and eosinophilic myelocytes, the composite histological picture being not unlike that of a polymorphous sarcoma. *The cause of the disease is totally unknown.* In certain quarters it is regarded as a variety of tuberculosis, but this origin has never been demonstrated, in spite of much investigation. It is possible that Hodgkin's disease, like the lymphosarcomata and multiple myelomata, represents a peculiar reaction to stimuli acting on functionally related tissues at the same or approximately the same time, the first effect of which, in Hodgkin's disease, is to promote hyperplasia of the lymphoid cells, and that the peculiar giant cells and the eosinophiles and eosinophilic myelocytes are derived from the bone marrow and are filtered out

by the hyperplastic lymph nodes. Clinically the disease first shows itself, as a rule, by enlargement of the cervical or other superficial groups of lymph nodes. There are, in addition, well defined varieties of Hodgkin's disease in which the changes are first manifested in other parts, as the thymic remains, the peribronchial lymph nodes, spleen, intestinal lymph follicles, etc.

Cohnheim (Virchow's Arch., 1865) described a disease under the title of **pseudo-leukemia,** characterized by marked hyperplasia of lymph nodes in various parts of the body but without increase in the number of circulating lymphocytes. This latter fact distinguishes it at once from chronic lymphatic leukemia, which presents virtually identical changes in the lymphoid tissues, but, in addition, is attended by enormous numbers of lymphocytes in the blood. Clinically, pseudo-leukemia cannot be distinguished from Hodgkin's disease except by microscopic examination of excised lymph nodes. From true leukemia it is at once differentiated, of course, by examination of the blood. In many quarters the term pseudo-leukemia still is erroneously employed as a synonym for Hodgkin's disease.

The neoplasmic disease described under the caption of **multiple myelomata** is characterized by foci of growth arising in different parts of the marrow system at approximately the same time, the individual tumors springing from certain primitive cells of the blood-forming series, variously described as lymphoblasts, neutrophilic myelocytes, erythroblasts, plasma cells and myeloblasts. It is highly doubtful, however, if there are myelomata composed of each of these varieties, but that all myelomata are made up of myeloblasts — in other words, the tumor is a *myeloblastoma.* The disease is rare. It occurs apparently exclusively in individuals over thirty-five years of age, oftenest in men, and pursues a rapidly fatal course. The bones involved are those with

FIG. 266.—(Bellevue Hospital.)   Mixed spindle and giant cell sarcoma of the upper end of the tibia.

red marrow, notably the vertebrae, sternum, ribs, skull, scapulae and ileum, and are exquisitely tender. Spontaneous fractures are common. The Bence-Jones albumose frequently is found in the urine in these cases. A notable feature of the myeloma consists in a tendency on the part of the growth to confine itself to the marrow system, although it may bring about continuate infiltration of adjacent structures by direct erosion of the bony casement. Genuine metastasizing myelomata are extremely rare, but do occur, cases having been recorded by *Christian* and *Symmers,* the metastases occurring in tissues having no relation either to bone marrow or to the extramedullary hemopoietic system. In still another group of cases, myelomata of the marrow are associated with identical growths in such tissues as the tonsil, spleen, lymph nodes and liver, but in these localities the tumor cells spring from or are implanted in tissue which is function-

ally related to bone marrow (*autochthonous myeloma*). Surgical intervention is sometimes necessary for the relief of mechanical symptoms, such as those produced by pressure on the spinal cord, but is otherwise hopeless.

There is another variety of medullary bone disease that has been variously designated *medullary giant cell sarcoma, giant cell myeloma, chronic hæmorrhagic osteomyelitis (Barrie), benign bone cysts*, etc. It is of great surgical importance. Two forms of growth are recognized — solitary and multiple, the latter having been described by *Martland*. In both forms the histology is the same; the lesion consists of medullary formations, in or near the ends of long bones, that are composed of innumerable giant cells of the osteoclastic type, imbedded in richly vascularized fibroblastic tissue, poor in mitoses, and associated with hæmorrhage and necrosis, the naked eye appearance of the growth being comparable to that of red-
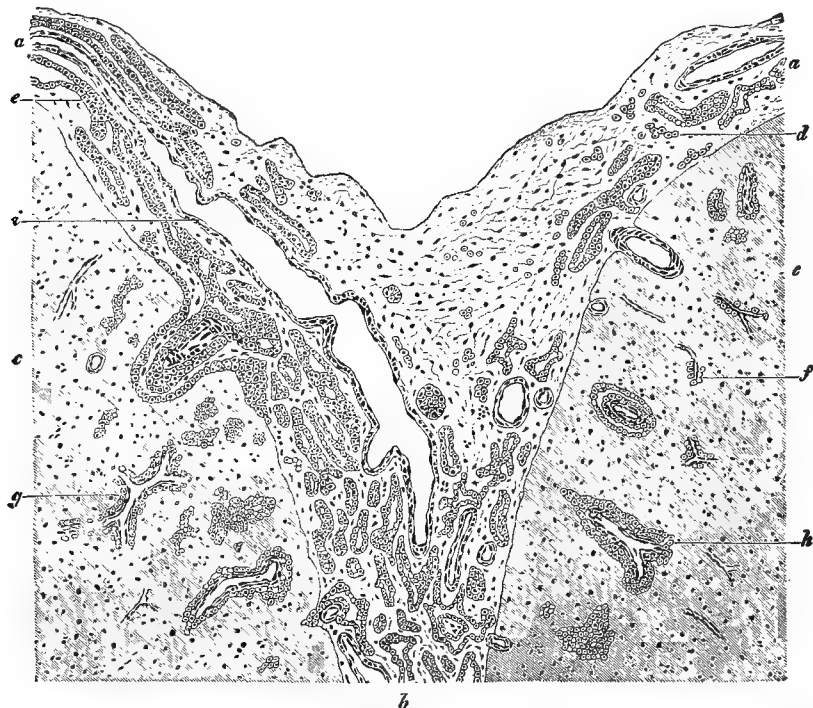
FIG. 267.— Section through an endothelioma of the pia mater and cerebral cortex, diffusely spread over the surface of the brain and spinal cord (Müller's fluid, hæmatoxylin). *a*, Superficial pia; *b*, pia in a sulcus; *c*, cortex; *d, e*, endothelial proliferations in the pia sheaths of the cortical vessels; *f, g, h*, endothelial proliferations in the pia sheaths of the cortical vessels; *i*, longitudinal section through a vein.   × 28.

currant jelly. Growth is expansive and slow, often stretching over a period of years, and the individual nodules are localized and circumscribed by relatively intact bone and periosteum. Infiltration of surrounding tissues and metastasis have not been observed, there is no Bence-Jones proteinuria, and the growths are painless. Spontaneous fractures are common. Simple curettement usually suffices, although local recurrence may take place. The multiple variety described by *Martland* constitutes a pathological entity with a close clinical resemblance to the multiple myeloblastomata already considered. It is obvious that differentiation of the two is important since, in *Martland's* disease, surgical intervention offers a hope of cure, and, in the solitary form, is distinctly promising. In this connection it is to be recalled, however, that mixed spindle and giant-cell sarcomata occur in the medullary ends of certain bones, notably the femur and tibia, that they grow expansively and rapidly and not uncommonly metastasize, and that the histology of these growths may simulate that of the formations described by *Barrie* and by *Martland*.

In such tumors, however, giant cells are less numerous and the stroma is more richly nucleated and poor in both intercellular substance and vascular channels, while mitotic figures are often discernible. When malignancy is fully established and flourishing, giant cells may be rare or wanting, the growth partaking of the nature of a pure spindle cell sarcoma. Three examples of this type of tumor have been encountered in the pathological laboratories of Bellevue Hospital in the past two years. In such cases, of course, amputation is imperative, all things else being equal. (Barrie, Annals of Surgery, 1913; Surgery, Gynecology and Obstetrics, 1914; Martland, Proceedings New York Pathological Society, 1915; Haussling and Martland, Annals of Surgery, 1916.)

§ 114. **Sarcomata which present an organoid structure** appear as **alveolar** and **tubular growths** in which it is possible to distinguish a *vascular connective-tissue stroma* and *strands* or *nests of cells*. According to their genesis, these growths may be divided into two types: *lymphangiosarcoma* and *hæmangiosarcoma*. There are, however, alveolar sarcomata which cannot be included with the above-named types.

The **lymphangiosarcomata** arise from *proliferation of the endothelium of lymph-vessels and lymph-spaces*. They may accordingly be designated
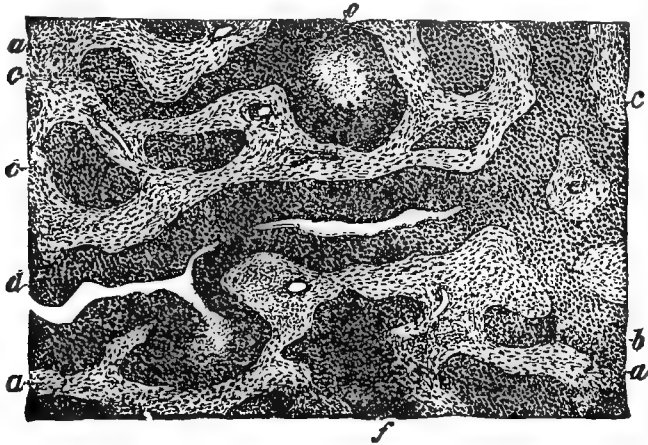
Fig. 268.—Endothelioma duræ matris (Müller's fluid, hæmatoxylin). *a*, Connective-tissue stroma; *b*, small-cell focus; *c*, groups and strands of cells arising from the proliferation of lymph-vessel endothelium; *d*, endothelial cell-strand with a lumen; *e*, area of fatty degeneration in nest of endothelial cells; *f*, strand of cells, passing gradually, on the right, into the surrounding connective tissue. × 25.

lymphangioendotheliomata or as *endotheliomata in the narrower sense*. They may develop in previously normal tissue, or in preëxisting tumor-like formations, such as the hypertrophic lymphangioma (pigmented moles and warts, see § 108), and from myxochondromata. The first occur particularly in the meninges of the brain, and in the serous membranes of the great body-cavities, but may develop in other organs; the second are found chiefly in the skin; those arising from myxochondromata develop in the salivary glands, palate, and orbit.

The *endotheliomata of the meninges of the brain and spinal cord* occur as nodular growths and as plaque-like proliferations; they develop through transformation of the flattened endothelium, which covers the connective-tissue of the subarachnoid tissue and pia, into cubical or cylindrical cells (Fig. 267, *d, e*). In consequence, the new-growth at first presents the appearance of *gland-like formations;* in the event of more active

proliferation solid *nests of cells* are formed. Inasmuch as the pia is continued as a lymph-sheath about the cerebral vessels, there are formed around the latter strands of large epithelial-like cells (Fig. 267, *f, g, h*).

Endothelioma of the dura mater arises through proliferation of the endothelium of the lymph-vessels, and leads, through filling of the latter with large cells, to the formation of anastomosing cords of cells (Fig. 268, *c, d, e*), which in places may contain a lumen.

Endotheliomata of the pleura or of the peritoneum appear as flattened thickenings of the affected membrane, but scattered nodular elevations may occur. These growths are characterized by cords of large cells

FIG. 269.— Endothelioma of the pleura (alcohol, hæmatoxylin). *a*, Proliferated and thickened pleural connective tissue; *b*, cell-strands. × 100.

(Fig. 269, *b*), which correspond to the course of the lymph-vessels in the serosa.

Endothelioma of the mammary gland is a rare tumor and takes its origin from proliferation of the endothelium of the lymph-vessels and lymph-spaces (Fig. 270, *b, c*), and gives rise to the formation of large cords of cells (*c*) or of smaller cell-nests. The proliferating cells are marked by great variation in the size, character, and form of the nucleus and cell-body.

Endothelioma of the skin, which arises from hypertrophic lymphangioma (warts and pigmented moles), resembles these in its general structure, and also possesses cell-nests of varying size (Fig. 246). Further, there occur endotheliomata of the skin, which do not arise from warts, and may develop in great numbers (Spiegler, Mulert).

The *endothelial proliferations which arise in myxomata and myxochondromata* form cords of cells of different shapes (Fig. 222, *b*); but it should be noted that in these cases similar proliferations may arise from the blood-vessels (Fig. 274, *c, d*), so that it is often impossible to decide as to the nature of the cell-strands.

The alveolar, tubular, or plexiform structure of the endothelioma is well marked only in the first stages of the tumor, and usually disappears with advancing growth. This is due to the fact that the endothelial proliferation extends, without sharp limits, into the neighboring connective
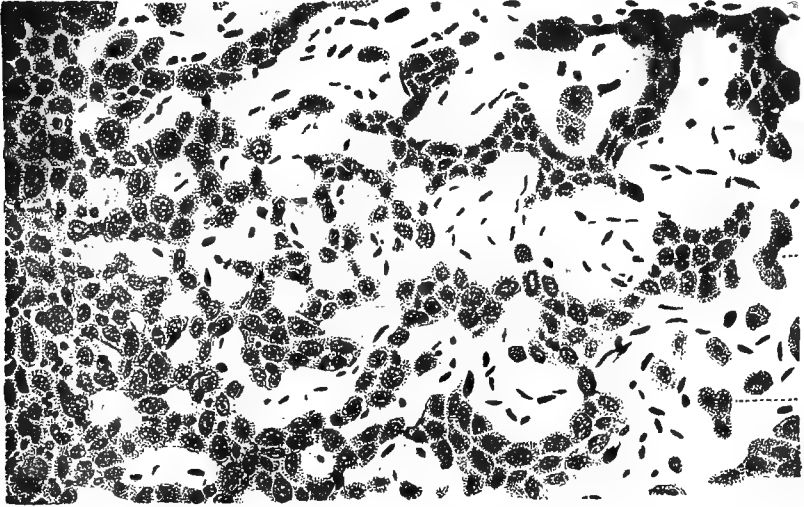
FIG. 270.— Endothelioma of the mammary gland (alcohol, hæmatoxylin, eosin). *a,* Connective tissue; *b,* enlarged cells in the connective-tissue spaces; *c,* strands of cells; *d,* diffuse cell-proliferation. × 300.

tissue (Fig. 268, *f*); and to the circumstance that the connective-tissue cells take on proliferative activity similar to that of the endothelium, so that there is formed a diffuse, cellular new growth of the character of an ordinary sarcoma (Fig. 270, *d*). Accordingly, endotheliomata cannot be sharply distinguished from sarcomata.
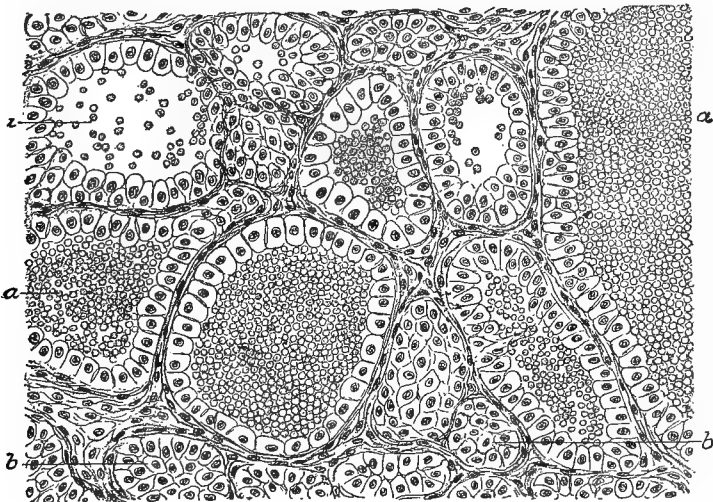
FIG. 271.—Blood-vessel endothelioma of the kidney (formalin, hæmatoxylin, eosin). *a,* Vessels filled with blood; *b,* vessels filled with proliferated endothelial cells. × 300.

The similarity in structure between endotheliomata and carcinomata raises the question whether it would not be expedient to class the former as *endothelial cancers.* The structure of these tumors would certainly justify such a classification, but I
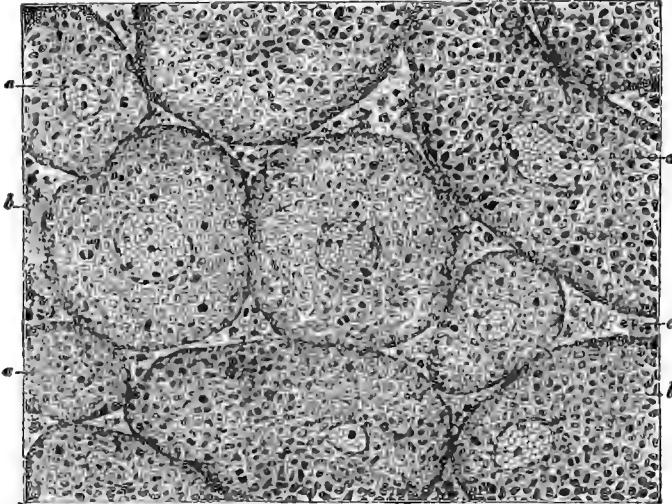
FIG. 272.— Section through a nodular angiosarcoma of the thyroid (Flemming's solution, safranin). *a*, Transversely cut vessels; *b*, perivascular cylinders of cells cut transversely and showing numerous mitoses; *c*, granular masses, with scattered cells, between the cell-cylinders. × 73.

consider it better to avoid the use of this term. In the first place, the term endothelioma is in general use and is entirely appropriate, and the introduction of the term endothelial cancer would easily give rise to confusion; by the term cancer
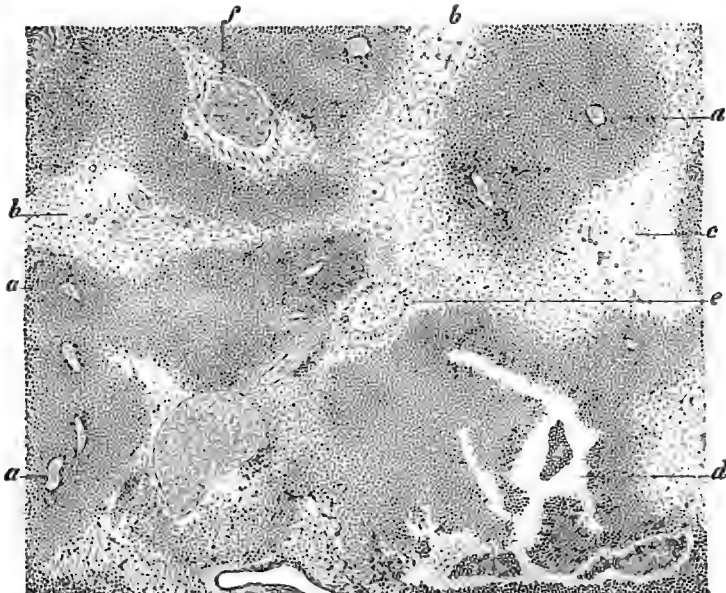
FIG. 273.— Angiosarcoma of the testis (Muller's fluid, hæmatoxylin, eosin). *a*, Perivascular masses of closely packed cells; *b*, areas poor in cells; *c*, hyaline lumps; *d*, hyaline masses containing blood; *e*, seminiferous tubules; *f*, large vein. × 80.

in general is understood an epithelial tumor, and it does not seem desirable to introduce two types of cancer — an epithelial and an endothelial.

I have classed as endotheliomata those tumors of the serous membranes which are characterized by the formation of cell-cords in the lymph channels, on the assumption that these arise from the endothelium of the lymph-vessels and lymph-spaces. I must admit, however, that I do not consider this assumption entirely justified, in spite of the concurring statements of a number of authors. The possibility of their development from the epithelium of the serosa is not excluded
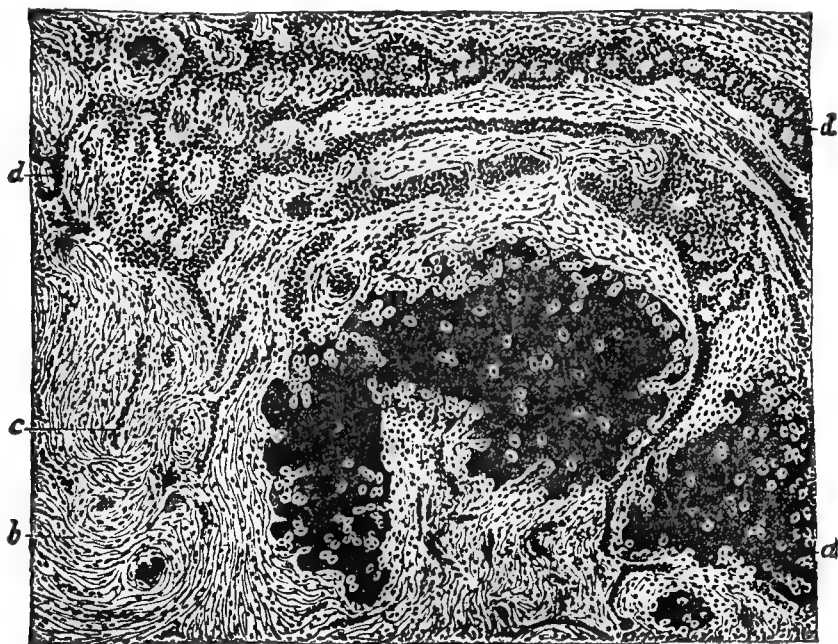
FIG. 274.— Chondrofibroma of the parotid with angiosarcoma (Müller's fluid, hæmatoxylin, eosin). a, Areas of cartilage; b, dense sarcoma tissue; c, blood-vessel; d, cell-strands arising from blood-vessels, and in part containing a hyaline substance. × 80.

(*Benda*), and if such an origin could be proved, the question would arise whether it would not be better to class these tumors with the carcinomata, since the corresponding tumors of the kidneys and ovaries, whose gland-cells arise from peritoneal epithelium, are classed with the epithelial tumors.

§ 115. The **hæmangiosarcomata** represent a group of organoid sarcomata in which blood-vessels constitute a characteristic feature.

One form of hæmangiosarcoma is the hæmangioendothelioma, a tumor which arises, either from preëxisting blood-vessels or from those newly formed in hæmangiomata, active proliferation giving rise to blood spaces lined with cubical or cylindrical endothelium (Fig. 271, a), or to canals completely filled with such cells (b). According to the number of blood-containing vessels the tumor is dark-red, pale, grayish-white or yellowish-white.

A second form of hæmangiosarcoma (occasionally called *perithelioma*), arises through proliferation of the outer layers of the blood-vessel walls and their immediate surroundings, so that the vessel-lumina are surrounded by a more or less thick mantle of cells (Fig. 272, b). In typical cases the tumor-tissue consists almost wholly of a tangle of blood-

vessels (Fig. 272, *a*), whose walls are banked by a thick layer of cells, which often reach to the endothelium. The cellular tubes sometimes run an isolated course, at other times anastomose, so that twistings and inter-
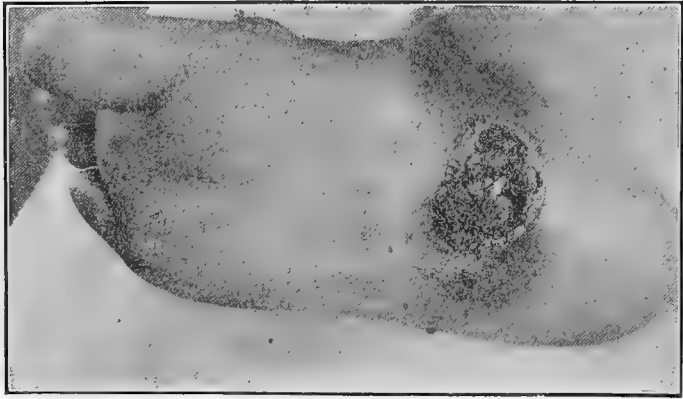
FIG. 275.—(Bellevue Hospital.)   Melanoma of instep.

weavings result (*plexiform angiosarcoma*). Between the cell-strands the remains of the original tissue (Fig. 273, *b*) may retain characteristic formations, for example, glands (*e*).

Should more active prolifera-tion of the perivascular mantle of cells occur, and if these become confluent (Fig. 273) the tumor passes into an ordinary sarcoma. This change almost invariably oc-curs in larger tumors of this kind.

Hæmangiosarcomata occur in various organs: testicles, kidneys, salivary glands, bones, brain, mamma, thyroid, skin, carotid gland, coccygeal gland, ovaries, and liver.

Lymphangiosarcomata   and hæmangiosarcomata cannot always be sharply differentiated from each other, and tumors occur to which both designations may be applied with propriety. The perivascular endothelial proliferation in the sub-stance of the brain associated with endothelioma of the pia (Fig. 267,

FIG. 276.—Alveolar melanotic sarcoma of the skin (alcohol, hæmatoxylin). *a*, Mononuclear, *a₁*, multi-nuclear sarcoma cells; *b*, pigment-con-taining cells; *e*, stroma with blood-vessels and pigment. × 300.

f, g, h) also justify the application of the term hæmangiosarcoma.

Borst, in his work on tumors, has separated the *endotheliomata* (lymphangio- and hæmangio-endothelioma) from the sarcomata, and has attempted to class them as a special form of neoplasm. In so far as typical microscopic pictures are concerned, such a separation is possible, but the endotheliomata in general do not show so typical a structure that they can be distinguished from ordinary sarcomata.

Further, it is by no means determined that endothelial cells of lymph spaces and vessels do not take part in the formation of sarcomata. It seems to me, therefore, better to consider the endotheliomata as a form of sarcoma.

§ 116. Sarcomata which acquire a peculiar character through special products of the cells or through changes in their ground-substance are to be found both among the simple and organoid forms. The chief types in this class are the melanosarcoma, osteosarcoma, osteoid sarcoma, the petrifying sarcoma, psammoma, and sarcomata containing hyaline formations.

Melanosarcomata occur in tissues which contain pigmented connective-tissue cells — *chromatophores.* They develop most frequently in the

FIG. 277.—Melanotic sarcoma of the skin (alcohol, carmine, eosin). *a*, Sarcoma tissue rich in cells; *b*, cell-nests; *c*, pigment-cells; *d*, blood-vessels with hyaline walls. × 300.

choroid of the eye and in the skin. In the latter situation they arise chiefly from pigmented moles. They belong to the malignant sarcomata, grow into neighboring tissues, and give rise to extensive metastases. The fully developed tumor is in whole or part smoky-gray, black or brownish-black, the color being due to the presence of round, angular, fusiform, and branched cells, which are filled with yellowish-brown pigment granules (Figs. 277, *b, e;* 278, *c*). In the alveolar forms both the large cell-nests, as well as the cells of the supporting framework, may contain pigment. It is often abundant in the neighborhood of the blood-vessels (Figs. 276, *e;* 277, *d*), although the pigment is not hæmosiderin.

The metastases are likewise more or less pigmented (Fig. 278); the smallest ones may consist largely of pigmented cells (*c, d*). Cases occur in which numerous organs, the skin, muscles, pia, serous membranes and adipose tissue (Fig. 278) are spotted black through the formation of metastases.

There is scarcely an individual who does not possess one or more skin moles, and every skin mole is a potential source of a milignant melanoma. The mole is
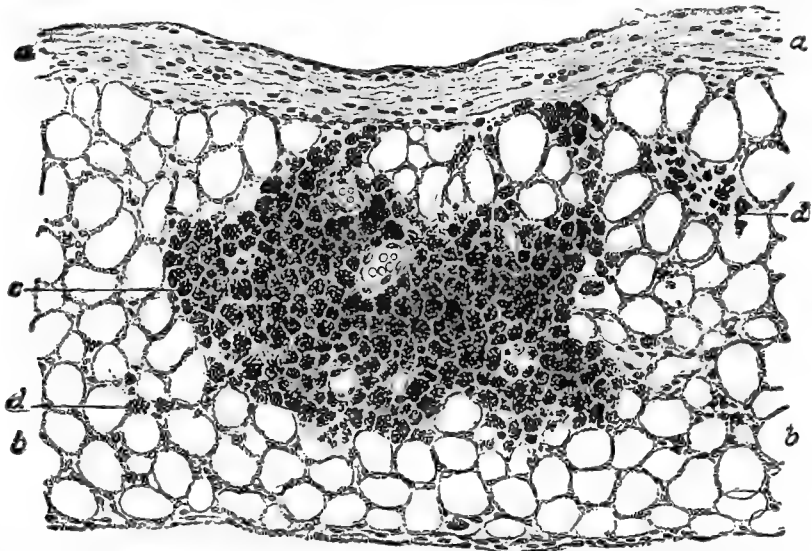
FIG. 278.— Metastasis of a melanotic sarcoma of the skin in the mesentery of the small intestine (formalin, alum-carmine). *a,* Peritoneum; *b,* fat tissue; *c,* sarcoma nodule; *d,* isolated chromatophores. × 280.

a vice of development characterized, even in the resting state, by a histological grouping of chromatophores that bears a striking resemblance to a malignant
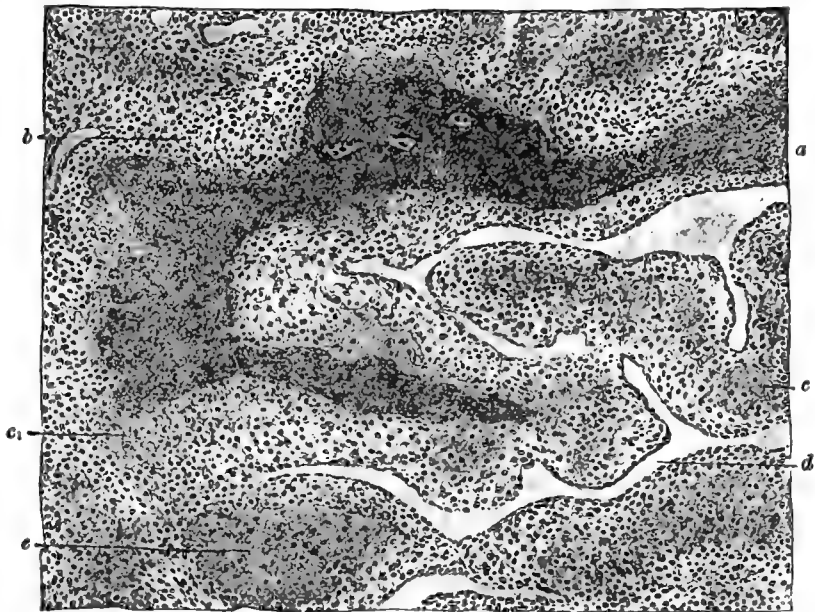
FIG. 279.— Endosteal osteosarcoma of the humerus. (Formalin, nitric acid, hæmatoxylin, and eosin). *a,* Old bony trabeculæ of the spongiosa; *b,* sarcomatous proliferation arising from the endosteum; *c, c₁,* new-formed bone; *d,* blood-vessel. × 80.

tumor. In fact, the number, formation and chromatic richness of the cells in many instances are such that a given microscopic field (Fig. 245) might readily be mistaken for a tumor with established malignant qualities instead of an appar-
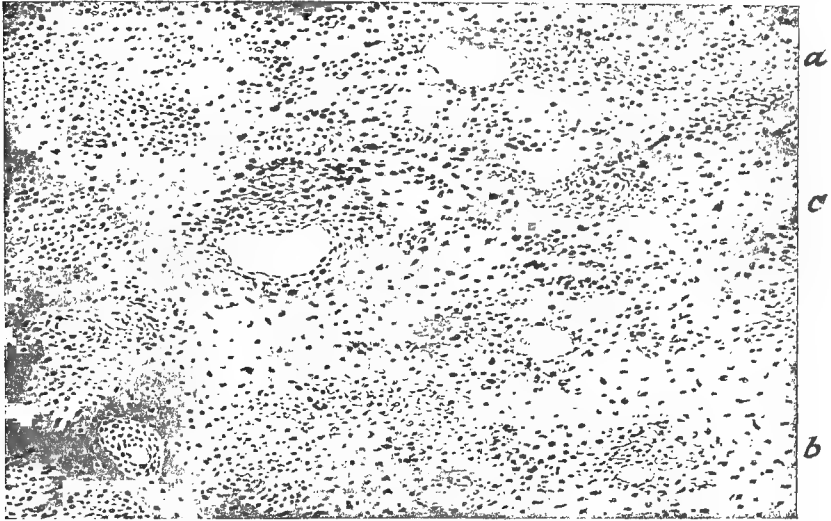
FIG. 280.—Sarcoma ossificans. (Formalin, nitric acid, hæmatoxylin, and picrofuchsin.) *a*, Sarcoma tissue; *b*, new-formed bone; *c*, areas of transition. × 40.

ently trivial congenital malformation of the skin. If left alone the skin mole may never occasion trouble, in fact, the vast majority maintain an attitude of innocent quiet. If, however, it is exposed to frequent irritation or, as not infrequently hap-
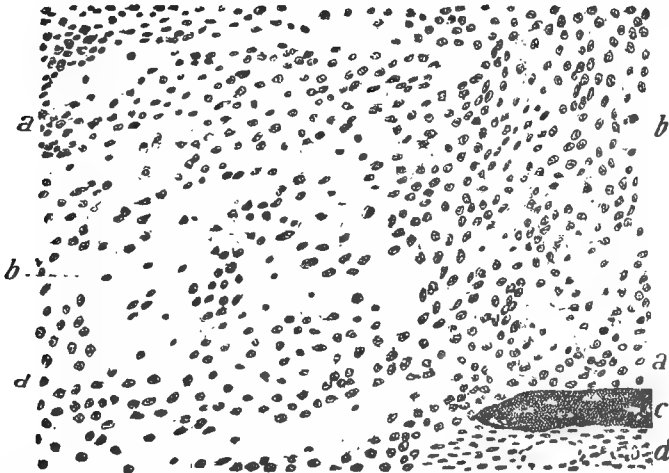
FIG. 281.— Osteoid sarcoma of the ethmoid bone (Müller's fluid, hæmatoxylin, eosin). *a*, Sarcoma tissue; *b*, osteoid tissue; *c*, old bone-trabeculæ; *d*, vascular fibrous tissue. × 45.

pens, it is deliberately subjected to ligation, escharotics, caustic salves, and the like, either at the hands of the host himself or of ignorant meddlers, it may develop into a growth of surpassingly vicious qualities. Moreover, malignant transformation

may occur soon after interference, or it may be postponed for months or years. In one of the Bellevue Hospital cases general melanomatosis followed the removal of a skin mole after the lapse of thirteen years. In other words, *the skin mole should be left to its own devices,* or, if removal is considered advisable, it should be done by a surgeon at the sacrifice of a considerable sweep of apparently healthy skin and subcutaneous tissue.

Osteosarcomata or **ossifying sarcomata** occur chiefly in connection with the skeleton and are characterized by the formation of bone in sarcomatous tissue. The new bone arises at times from a homogeneous

FIG. 282.—Petrifying large-cell sarcoma of the tibia (Müller's fluid, hæmatoxylin, eosin). *a,* Polymorphous tumor-cells; *b,* alveolar stroma; *c,* trabeculæ of stroma containing small calcareous concretions; *d,* petrifying trabeculæ of the stroma. × 330.

ground-substance Fig. 279 (*c, c$_1$*) formed between the tumor-cells (*b*) which is either connected (*c$_1$*) with the old bony trabeculæ (*a*) or arises independently (*c*), or at other times from coarsely fibrillated connective tissue (Fig. 280, *c*) which gradually becomes condensed (*b*) and, taking up lime-salts, is transformed into bone.

Osteoid sarcomata develop in the endosteum and periosteum, and are characterized by thickening of the ground-substance in certain areas, forming *trabeculæ of osteoid tissue* (Fig. 281, *b*). Such tumors are closely related to the osteosarcomata, but differ from them in the absence of lime-salts.

Petrifying sarcomata likewise occur most frequently in connection with the skeleton, and are characterized by the development between the tumor-cells of a ground-substance (Fig. 282, *c*), through *calcification* (*d*) of which the tumor tissue becomes hardened, although no typical bone is formed.

FIG. 283.—Section from a psammoma of the dura mater (alcohol, picric acid, hæmatoxylin, eosin). *a,* Hyaline nucleated spherule inclosing calcareous concretion; *b,* calcareous concretion with hyaline non-nucleated border, inclosed in fibrous connective tissue; *c,* calcareous concretion surrounded by hyaline connective tissue; *d,* spicule of lime in the connective tissue; *e,* spicule with three concreitions. × 180.

Psammomata or *sand tumors* are sarcomata or fibro-sarcomata of the dura, inner meninges, or pineal gland, which contain *concretions of lime-salts* in greater or less abundance. Some of these concretions are
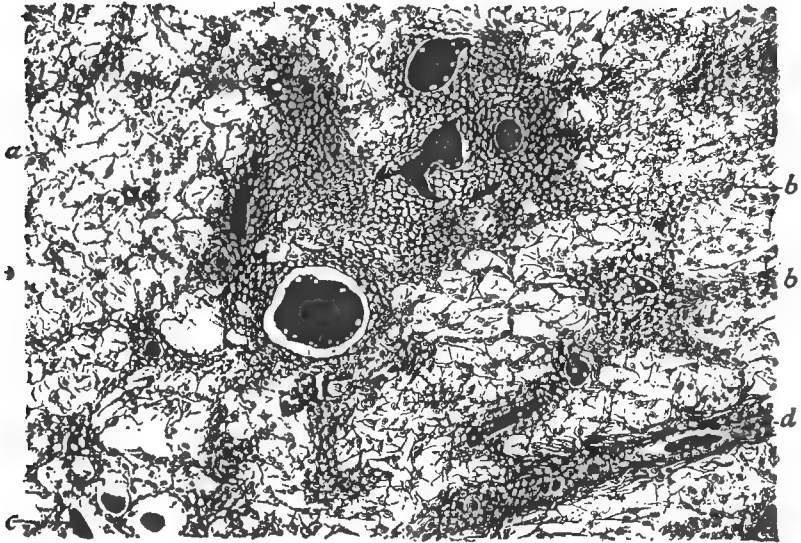
Fig. 284.— Myxo-angiosarcoma of the parotid, with hyaline formations (Müller's fluid, hæ-matoxylin, eosin). *a*, Myxomatous tissue; *b*, cell-strands inclosing hyaline spherules; *c*, hyaline spherules in myxomatous tissue; *d*, blood-vessels with proliferating endothelium and hyaline spherules. × 90.

similar in structure to the normal brain-sand, the basis of their formation being concentric layers of cells which have previously undergone hyaline degeneration (Fig. 283, *a*, *b*, *c*). Occasionally the chalky spherules lie inside individual cells and represent hyaline products of the cells that
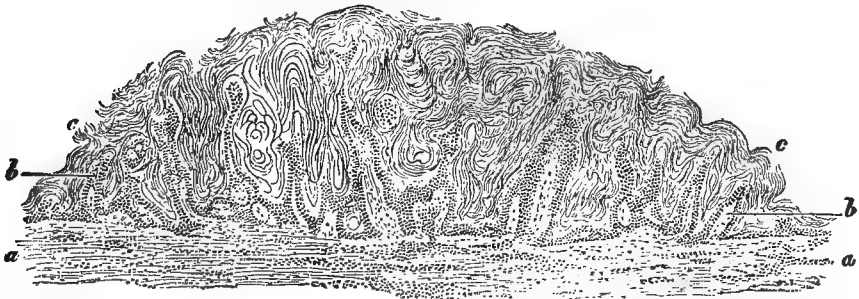
Fig. 285.— Papillary epithelioma or ichthyotic wart of the skin (Müller's fluid, hæmatoxylin, eosin). *a*, Corium; *b*, enlarged papillary body; *c*, laminated horny layer. × 25.

have become calcified. Others are of the nature of spicules (*d*), and arise through the deposit of lime-salts in connective tissue or blood-vessels which have undergone hyaline degeneration.

Psammomata usually form round nodules, and are often multiple.

Sarcomata with hyaline formations (the myxosarcomata excepted) arise as follows: *Either the cells form hyaline products, or they themselves become converted into such, or the fully developed connective tissue and the blood-vessels undergo hyaline degeneration.* These changes may take place in simple sarcomata as well as in endotheliomata and hæmangiosarcomata; but occur more frequently in the latter (Figs. 280, *b;* 274, *d;* 284). The hyaline masses form spherules, or club-like forms, or cords, or net-like or cactus-like figures. They push the cells apart, and often reduce them to narrow strands. Billroth has designated such
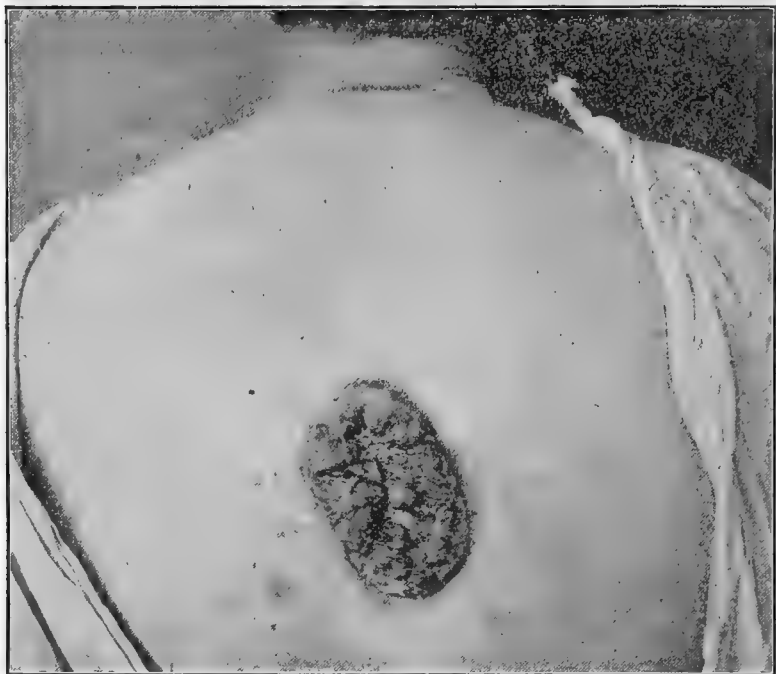
Fig. 286.—(Bellevue Hospital.)   Papillary epithelioma of back.

tumors *cylindromata.* In endotheliomata hyaline degeneration may be associated with the formatin of *laminated masses of flattened cells* around a nucleus, like the layers of an onion.

Hyaline degeneration of the vessel-walls and connective-tissue bundles results in thickening, (Fig. 277, *d*), sometimes uniformly and sometimes irregularly distributed. *Hyaline products of cells* have a tendency to assume spherical form (Figs. 269, *b;* 274, *d;* 284, *c, d*). The disintegration of larger cell-masses with hyalinisation leads to the formation of spherules, strands, or branching structures.

If, in endotheliomata and angiosarcomata, the cord-like masses of cells in the lymph- or blood-vessels become converted into hyalin, structures arise which resemble glands containing colloid (Fig. 284, *d*) and have often been mistaken for such.

2. The Epithelial Tumors.

(a) *General Remarks.*

§ 117. The **epithelial tumors** are new growths in the formation of which vascular connective tissue and cells derived from surface or glandular epithelium take part. The distribution of epithelium and connective tissue follows, in a general way, the normal arrangement of these tissues, the connective tissue forming a basement structure covered with epithelium (skin and mucous membranes), or a stroma, in the meshes of which the epithelial cells are distributed in gland-like array. The imitation of skin structure leads to the formation of **papillary new-growths**; that of mucous membrane, to more of less sharply circumscribed **nodules** or to **extensive superficial thickenings of tissue.**
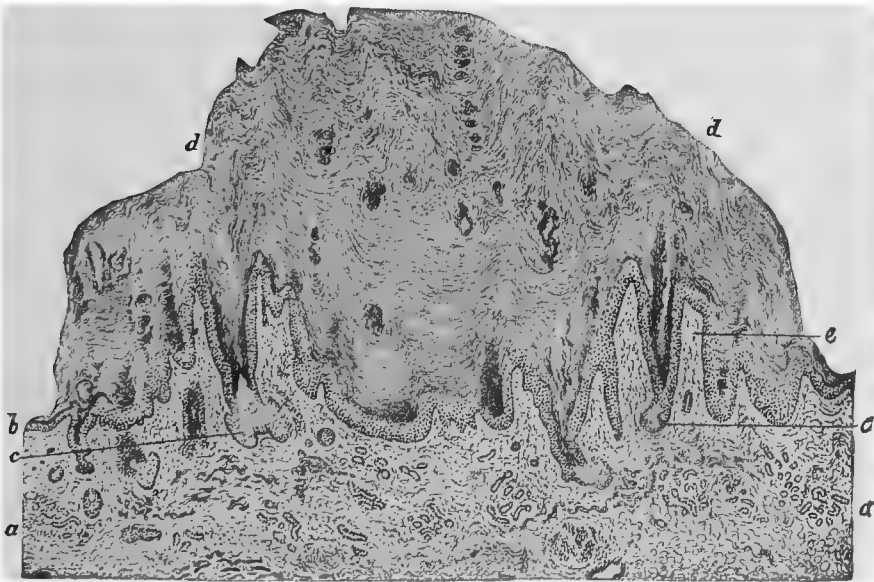
Fig. 287.— Senile horny wart of forehead, from a woman eighty-four years of age (alcohol, hæmatoxylin, eosin). *a,* Corium; *b,* epithelium; *c,* atrophic sebaceous glands with development of horny epithelium in their ducts; *d,* hypertrophic horny layers; *e,* enlarged papillæ. × 15.

According to the physical characteristics and arrangement of the epithelial cells, as well as the clinical behavior of these tumors, epithelial new-growths may be divided into two groups; one including **papillary epitheliomata, adenomata,** and **cystadenomata;** the other **carcinomata** and **cystocarcinomata.** The first group is characterized clinically by the benign character of the growths, *which are sharply circumscribed* and form *no metastases.* The second group includes new-growths *which infiltrate and give rise to metastases.* The two groups, however, are not sharply separated, as papillary epitheliomata and adenomata may, through changes in the mode of reproduction and spread of the epithelial cells, become changed into carcinomata.

(b) Papillary Epithelioma, Adenoma, and Cystadenoma.

§ 118. A **papillary epithelioma** is a new-growth composed of a framework of connective-tissue papillæ covered with epithelial cells. In structure, therefore, it is similar to the papillæ of the skin; but the papillæ are, as a rule, higher and often branched, and the epithelial covering thicker.

The **papillary epithelioma** of the skin occurs in the form of *warty protuberances,* which consist of slender papillæ (Fig. 285), covered with epithelium, the superficial layers of which show marked cornification (*ichthyotic warts* and *horny warts*). These warts may appear during childhood (*ichthyotic warts*) or in old age (*ver-*
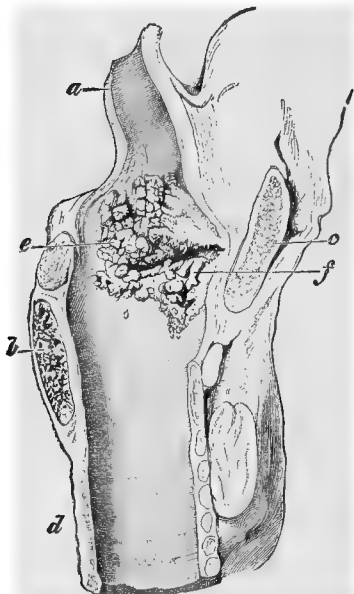
FIG. 288.

FIG. 289.

FIG. 288.— Papillary epithelioma of the larynx. *a*, Epiglottis; *b*, ossified cricoid cartilage; *c*, thyroid cartilage; *d*, trachea; *e*, *f*, papillary proliferations. Natural size.

FIG. 289.— Papillary epithelioma of the urinary bladder. *a*, Epithelioma; *b*, *c*, enlarged prostate; *d*, thickened bladder-wall. Five-sixths natural size.

ruca senilis). The first-named represents a local malformation of the skin (Fig. 285); while the latter is due to pathological proliferation and cornification of the epithelium (Fig. 287, *c, d*) followed by outgrowth of the papillæ at the periphery. Excessive cornification of epithelium over hypertrophic papillæ, giving rise to cylindrical or conical masses of cells in which the horny layers lie at right angles to the surface, leads to the formation of a *cutaneous horn or cornu cutaneum* (Figs. 112, 113).

Papillary epitheliomata of mucous membranes occur as warty, nodular formations (Fig. 288, *e, f*), or as long, slender papillary excrescences (Fig. 289, *a*), which, springing from a narrow base, are often repeatedly branched. The former variety is found especially in the larynx, more rarely in the nose and urinary bladder; the latter in the urinary bladder and pelvis of the kidney, vaginal portion of the uterus, and rarely in the ureters, gall-bladder, and biliary passages.

In both varieties the excrescences are formed of slender, connective-tissue papillæ (Fig. 290) which contain blood-vessels, and are covered by a thick layer of epithelium the character of which corresponds in
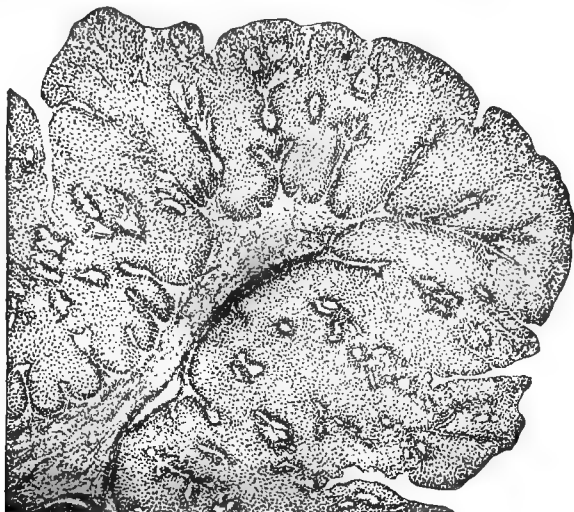
Fig. 290.— Papillary epithelioma of the urinary bladder (alcohol, hæmatoxylin, eosin). × 35.

general to that of the part in which the growth occurs, although papillomata covered with stratified squamous cells are sometimes seen in regions that normally possess cylindrical epithelium (nose, trachea).

Papillary epitheliomata in cysts, or so-called **papillary cystomata,** occur most frequently in cysts of the ovary and of the mammary gland, more rarely in the skin. Within the cyst are formed small, warty elevations or cauliflower-like outgrowths, which may fill the entire cyst-cavity.

Papillary epitheliomata of the surface of the ovary appear in forms similar to those of the urinary bladder, but are rare. **Papillary epitheliomata of the cerebral ventricles** rise in part from the telæ choroideæ.

It is difficult to draw a line between **papillary epitheliomata** and other formations. Inflammatory proliferations of the skin and mucous membranes — **pointed condylomata** — which develop on the external genitals under the influence of chronic irritation (compare Fig. 246), so closely resemble epitheliomata that their inflammatory origin forms the only point of difference. If the connective-tissue framework of the papillary outgrowth is developed to a greater extent than the epithelium, the tumor may be classed with the **papillary fibromata,** and it becomes a question of individual standpoint as to which designation shall be employed. Intermediate forms can be designated as **papillary fibroepitheliomata.** Finally, the benign papillary epitheliomata may pass into **carcinomata,** either through the growth of epithelium at the base of the papillæ

into the underlying connective tissue, or through extension of the proliferating surface epithelium into neighboring organs (as in the papillary epitheliomata of the ovary).

Among the epitheliomata may be classed those formations known as **cholesteatomata** or **pearl tumors,** which in part are caused by inflammation, and in part represent misplaced embryonal tissue. The most striking characteristic of the cholesteatoma is the formation of glistening white pearls, which consist of thin, scale-like epithelial cells pressed closely together, and which often inclose cholesterin. These tumors are found most frequently in the descending urinary passages, the cavities of the middle ear, and the pia of the brain; rarely in the spinal cord.

Pathological cornifications, with the formation of glistening white scales and pearls, occur in the *urinary passages,* particularly in the course of chronic inflammations. In the *tympanic cavity, mastoid antrum,* and *external auditory canal,* the cholesteatomata appear as yellowish-white or bluish-white nodules, varying in size from a cherry-stone to that of an egg, and presenting an onion-like laminated structure. Through pressure on neighboring bone they may cause its disappearance. In chronic inflammatory conditions they arise as a product of squamous epithelium which has penetrated from the external ear through openings in the ear-drum into the cavities of the middle ear and has replaced the cylindrical epithelium. It is probable that in rare cases they arise from epidermoidal cells which during the period of embryonic development have found their way into the cavities in question.

The *intracranial cholesteatomata* are found at the base of the brain (rarely in the spinal canal), in the region of the olfactory lobe, tuber cinereum, corpus callosum, in the choroid plexus, in the pons, medulla oblongata, and cerebellum. In these regions the cholesteatomata appear on the surface as silk-like, shining nodules of varying size which extend more or less deeply into the brain-substance. The nodules are single, but cholesteatoma-masses may become separated and be displaced into neighboring tissue. According to *Boström,* it is always possible to demonstrate, at some point, a connection between the pia and the cholesteatoma, where the scales composing the cholesteatoma take their origin from a cell-layer lying on vascular connective tissue, the cells throughout bearing the character of epidermoidal cells. The cholesteatomata of the pia may therefore be designated as *epitheliomata* or as *epidermoids (Boström)* ; and their origin may be explained by the assumption that in the early period of development epidermal germs are misplaced into the primordium of the pia.

§ 119. The **adenomata** are usually *nodular tumors* with sharply defined borders; and are situated in glands, or in the skin or mucous membranes. In the latter situations they frequently appear as polypi elevated above the surface. They may also occur in the form of papillary proliferations (Fig. 211). The absence of any tendency to grow by infiltration or to produce metastases stamps these tumors as *benign.*

The chief characteristic of the adenoma is the *formation of new glands,* which depart more or less from the typical glands of the affected organ. According to their structure adenomata may be classed as *tubular* or *acinous;* but the two forms cannot be sharply separated. Through the formation of papillary excrescences on the inner walls of the gland-spaces there is formed an *adenoma papilliferum. Adenomata develop in apparently normal tissue, malformed tissue, in tissues altered by disease* (chronically inflamed mucous membrane, cirrhotic liver, contracted kidney), or from *remains of fœtal structures.* The new-formation of glands is dependent on proliferation of glandular epithelium similar to that occurring in regeneration of normal gland-tissue. The beginning of the adenomatous process may be recognized by changes in the form and staining of the cells. This is particularly true of the stomach and intestine, in which adenomatous proliferations often develop in connection with chronic inflammatory and ulcerative processes. The change of normal gland-cells into high cylindrical cells may occur contemporane-

ously or successively in a number of glands and is followed by cell-proliferation and new-formation of glands.

The cause of the new-formation of gland-tissue in normal organs is
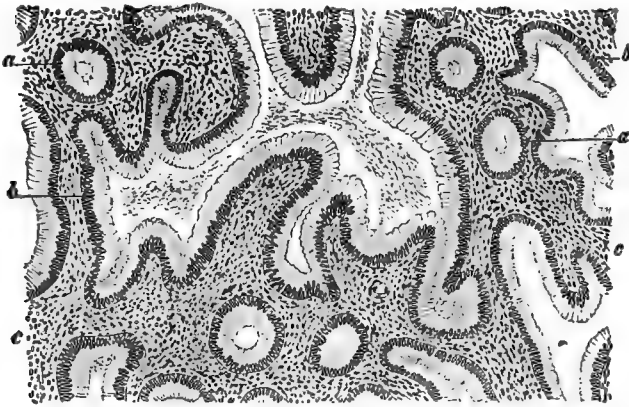
FIG. 291.—Adenoma tubulare (glandular polyp) of the intestine (alcohol, alum-carmine). *a*, Transverse section, *b*, longitudinal section of gland-tubules; *c*, stroma rich in cells. × 90.

unknown. Glandular new-formations developing in tissues which have been altered by inflammation, and which lead to tumor-like growths, may, in the beginning, bear the character of a regenerative or hyperplastic new-
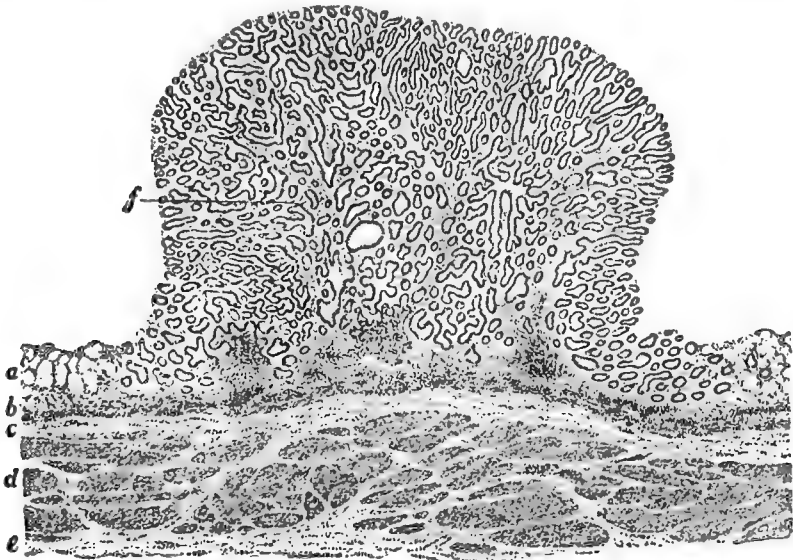
FIG. 292.—Adenoma tubulare of the stomach in an atrophic mucosa (formalin, alcohol, hæmatoxylin, eosin). *a*, Mucosa; *b*, muscularis mucosæ; *c*, submucosa; *d*, muscularis; *e*, serosa; *f*, adenoma. × 14.

formation, and for this reason the *adenomata cannot be sharply differentiated from regenerative and hyperplastic proliferations.*

Tubular adenomata represent the most common form. They occur

particularly in mucous membranes (Fig. 291, 292, f) provided with tubular glands (intestine, uterus); but are also found in the breast (Fig. 293), liver, ovary, and not infrequently in the kidneys. They are characterized
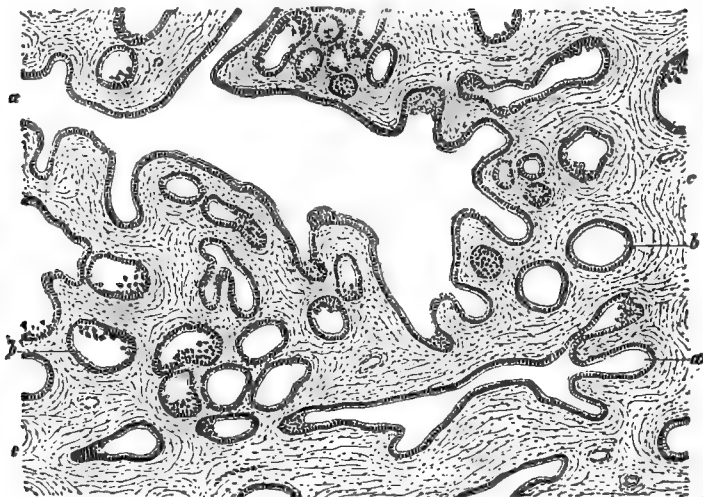
Fig. 293.—Adenoma mammæ tubulare (alcohol, alum-carmine). *a*, Branched and dilated glandular spaces cut longitudinally; *b*, same, cut transversely; *c*, stroma. × 27.

by the formation of simple and branched tubules (Figs. 291, *a*, *b*; 292, *f*; 293, *a*, *b*) lined by columnar or cubical epithelium and form nodular tumors varying in size from a pea to that of an apple or a man's fist, or even larger.
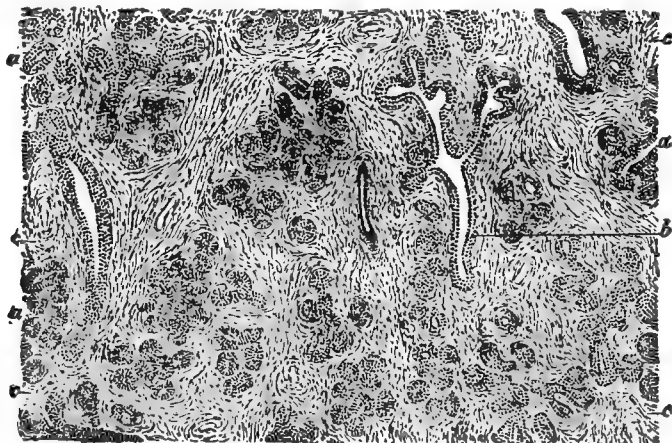
Fig. 294.—Adenoma mammæ alveolare (alcohol, alum-carmine). *a*, Terminal alveoli; *b*, gland-ducts; *c*, connective-tissue stroma. × 27.

The **alveolar adenomata** arise from glands (mamma, ovary, thyroid, sebaceous glands); and are characterized by the formation of numerous terminal berry-like alveoli (Fig. 294, *a*), as well as ducts (*b*).

Papillary adenomata (Fig. 295, *a*) arise through the formation in the tubules of an adenoma of elevations of epithelium into each of which a connective-tissue papilla grows.
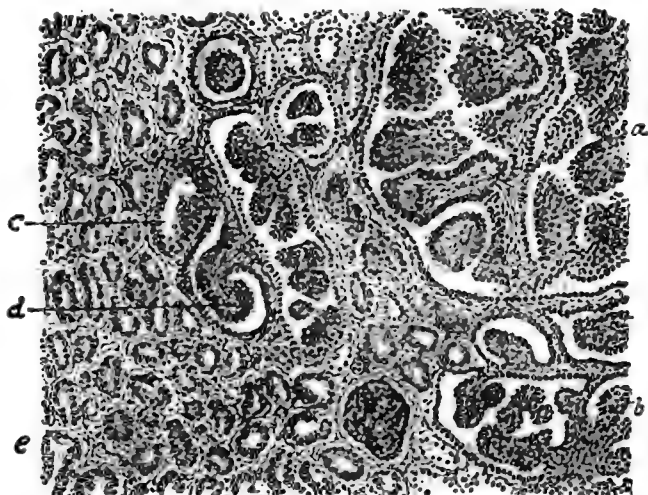
FIG. 295.— Developing papillary adenoma of the kidney. (Alcohol. hæmatoxylin, picrofuchsin.) *a, b*, Fully developed tumor-tissue; *c, d*, early stages of development of the tumor. × 150.
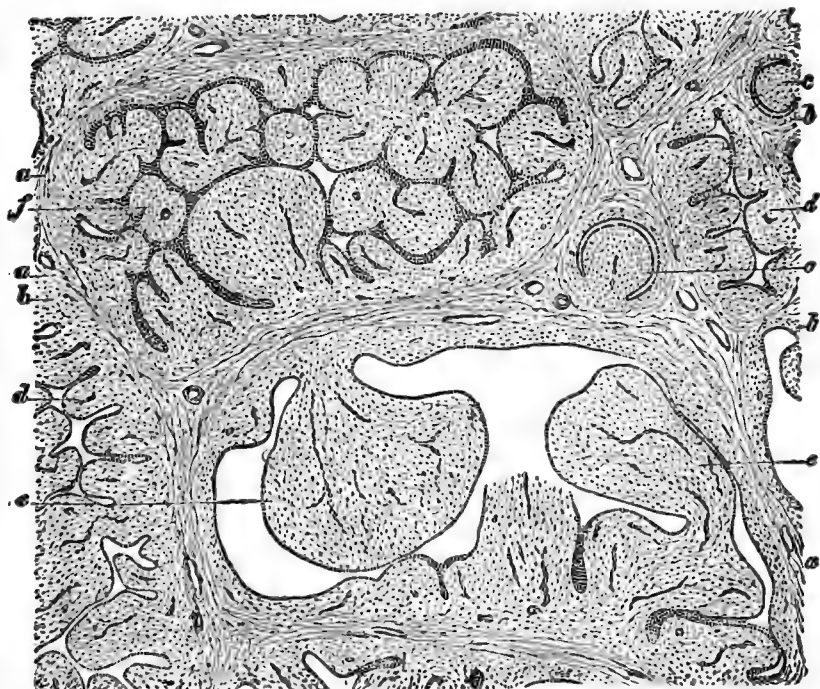
FIG. 296.— Fibroma intracanaliculare mammæ (fibro-adenoma papilliferum) (alcohol, alum-carmine). *a*, Dense, intercanalicular growth of fibrous tissue; *b*, pericanalicular tissue rich in cells; *c, d, e*, nodular intracanalicular connective-tissue proliferations cut longitudinally; *f*, intra-canalicular proliferations cut transversely. × 23.

The **stroma of an adenoma** is at times well developed, at other times but slightly. Consequently adenomata may be divided into *hard* (mammary gland) and *soft varieties* (kidney, liver, ovary, testicle). Marked development of the connective tissue leads to the formation of **fibro-adenomata** or *fibrous adenomata*. Such forms occur most frequently in the mammary gland.

If, as happens not infrequently in the mammary gland, the connective-tissue proliferation in an adenoma is not of diffuse character, but takes place more particularly around the canaliculi (see Fig. 220), the tumor is designated *fibroma pericanaliculare*. If, as the result of more marked local proliferative activity on the part of the connective tissue (Fig. 296, *c, d, e*), an ingrowth of papillæ (*e*) into the gland-spaces takes place, the resulting tumor is known as a **fibroma intracanaliculare.**

FIG. 297.—Section of a cystadenoma ovarii papilliferum (Müller's fluid, hæmatoxylin). × 40.

Adenomata cannot be sharply differentiated from tumor-like glandular hypertrophies on the one hand, and carcinomata on the other. For example, in the healing of intestinal ulcers regenerative processes in the glands may be so active as to give rise to polypoid formations, which may be called *glandular hypertrophies* or *adenomata,* according to the individual standpoint. Likewise, different names may be applied to the glandular polypi which occur so frequently in the uterus.
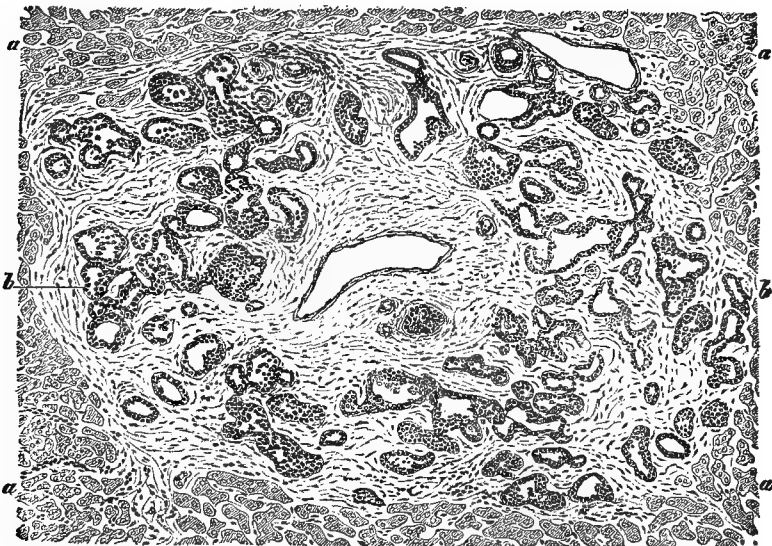
FIG. 298.—Adenocystoma of the bile-passages in the first stages of development (alcohol, hæmatoxylin). *a,* Liver tissue; *b,* adenoma tissue in the periportal connective tissue. × 90.

The *carcinomatous nature* of a new-growth resembling an adenoma (see § 121) is generally made evident by more marked epithelial proliferation and by infiltrative growth. There are, however, adenomata having a single layer of columnar cells, that grow by infiltration (particularly in the intestine), and assume the character of malignant tumors. They should accordingly be classed with the carcinomata, and must be designated *adenocarcinoma*. On the other hand, there are also adenomata with marked atypical epithelial proliferation (mamma, endometrium), which — for a long time at least — do not show any malignant characteristics.

§ 120. A **cystadenoma** or **adenocystoma** is an *adenoma whose gland-spaces have undergone cystic dilatation through the accumulation of secretions*. Such tumors are usually composed of numerous cysts, and are, therefore, designated **multilocular cystomata.** According to the character of the wall there may be distinguished a *simple* and a *papilliferous cystoma.*

Small amounts of secretion are often seen in the ordinary adenomata
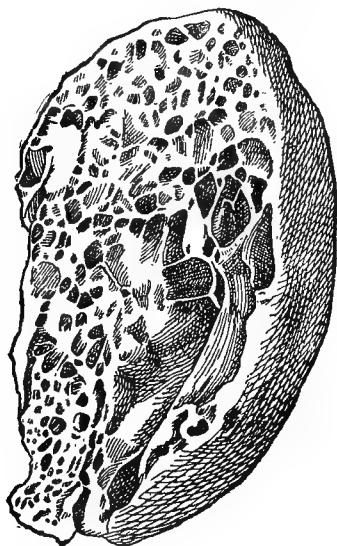
FIG. 299.   FIG. 300.

FIG. 299.— Section of a portion of a multilocular adenocystoma of the ovary. Reduced about one-sixth.
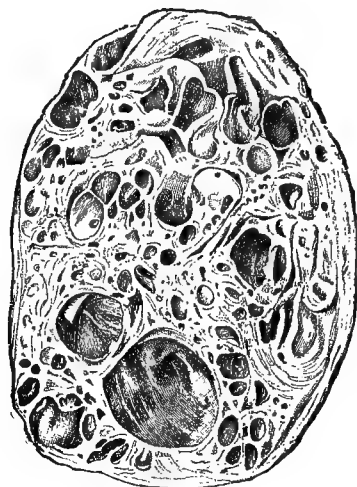
FIG. 300.— Section through an adenocystoma of the testis of a four-year-old boy. Natural size.

(Fig. 291), and the spaces of both simple and papillary adenomata are often so wide (Figs. 293, *a;* 296) that they attract the eye on cross-section of the growth. In cystadenomata cyst-formation is the predominating feature.

The early stages of the cysts are represented by *gland-tubules* of varying shape (Figs. 297 and 298, *b*), that lie in a more or less richly developed connective-tissue stroma. Through the accumulation of secretion these tubules become gradually dilated so that numerous small cysts (Fig. 297), or both large and small cysts (Figs. 300-303) are formed. Often the relationship is such that the tumor may consist of a few large cysts in which smaller cysts occur; or there may be found, by the side of large cysts, (Fig. 301, *c*) portions of tissue which contain only small cysts (*e*) or even appear solid — that is, consisting of tissue the glands of which are not dilated.

All the different varieties of cystomata may develop in the ovaries (Fig. 299), testicles (Fig. 300), liver (Figs. 298 and 301), kidneys (Fig. 302), and the mammary glands.

In the ovaries cystomata not infrequently develop coincidently on both sides, and may be associated with dermoid formations. Adenocystomata of the testicles not infrequently inclose in their stroma foci of cartilage or other tissue, so that such growths should be classed with the *teratomata* (§ 128).

The *epithelial lining of cystomata* is usually composed of simple columnar cells, but may be ciliated, cubical, or flattened.

The cyst-contents usually consist of clear, often ropy fluid, which contains a mucin-like substance (pseudomucin, see § 59). This is a product
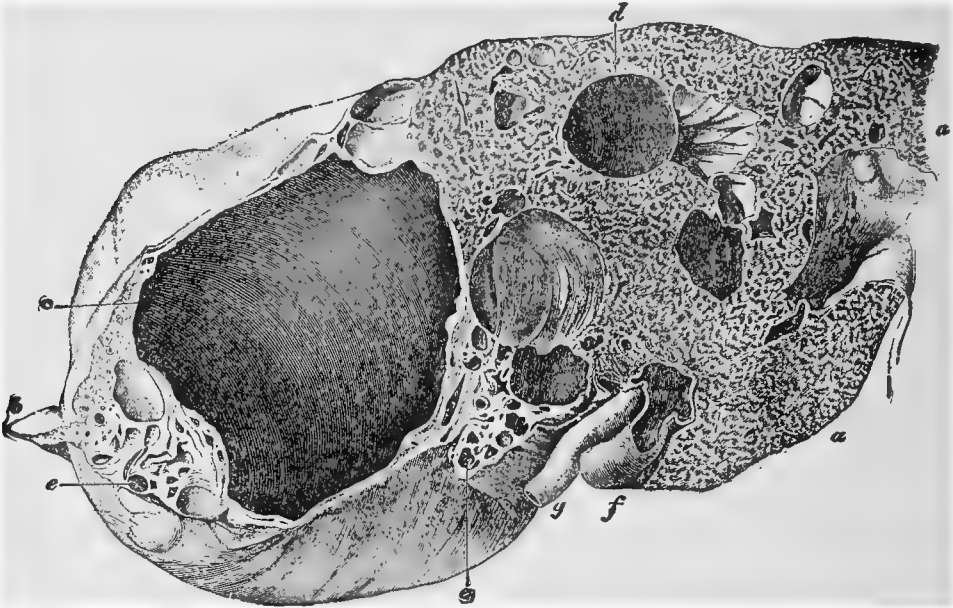
Fig. 301.— Multilocular adenocystoma of the liver, seen in section. *a*, Liver parenchyma; *b*, membranous margin of the left lobe; *c*, *d*, large cysts; *e*, group of smaller cysts, separated from each other only by connective tissue; *f*, portal vein; *g*, hepatic artery. Two-thirds natural size.

of the epithelial lining in which goblet-cells are found (Fig. 304, *c*). Not infrequently the fluid contains whitish flakes, the products of cells which have undergone fatty degeneration; or it may be more or less reddish or brownish from previous hæmorrhage. Abundant secretion in multiple cysts may lead to tumors of enormous size; in the ovary, for example, they may reach a weight of from ten to twelve kilograms or more.

The **papillary adenocystomata** constitute a common variety. They are characterized by the fact that sooner or later papillary excrescences develop in glands which have undergone cystic dilatation.

In the adenocystomata of the ovary such excrescences are usually slender and delicate, forming villous-like (Fig. 303) or cauliflower elevations, which fill a larger or smaller part of the cysts. Minute papillary elevations, extending over an extensive area of the inner surface of the cyst-wall, may give to the latter a velvety appearance similar to that

of a mucous membrane. If the excrescences develop in cysts of small size, they may fill these, and the tissue may take on the appearance of a medullary tumor.

Larger papillæ are always more or less branched (Fig. 304), and consist of a cellular stroma (a), whose surface is covered with tall cells (c) of the character of goblet-cells. The contents of the cysts consist of ropy mucus (d) mingled with desquamated cells which have undergone mucous degeneration. In rare cases the connective tissue of the papillæ

FIG. 302.— Cystoma of the kidney, cut transversely. Eleven-fourteenths natural size.

may undergo mucous degeneration (Fig. 305, a, b), and swell to a marked degree, and finally become changed into myxomatous spheres covered with epithelium.

Adenocystomata of the liver, testicles, and kidneys usually form no papillæ, or at most small ones. In the papillary adenocystomata of the mammary gland the excrescences are broad and plump (Fig. 306), as are those of the papillary adenomata (Fig. 296). Accordingly, on cross-section the cyst-spaces are found to be filled with polypoid proliferations of various forms (Fig. 306), which are flattened through mutual pressure, and give to the cut surface a laminated appearance.

Since in these tumors the connective-tissue elements predominate over the epithelial, these growths are often classed with the *connective-tissue tumors*, and designated, according to the character of the connective tissue, *cystofibroma, cystomyxoma,* or *cystosarcoma.* When showing a structure of leaf-like layers they receive the name of *sarcoma phyllodes.*

The *papillary adenocystomata* show a *certain degree of malignancy.* The papillary proliferations may break through the cyst-wall in such tumors of the ovary and mammary gland; in the latter situation they may break through the skin. Papillary ovarian cystomata in this way give rise to metastases in the peritoneal cavity.

Polycystic degeneration of the kidneys is an affection which leads, during embryonal development, to the formation of innumerable cysts throughout both organs, and frequently is associated with the presence of cysts in the liver and other anomalies of growth. The occurrence of renal cysts in these circumstances is apparently due to the fact that the kidney is developed from two primordia, one giving rise to the glomeruli and convoluted tubules and the other to the straight and collecting tubules. Failure of the two primordia properly to unite permits cystic distention of the glomerular capsule and of the convoluted tubules.
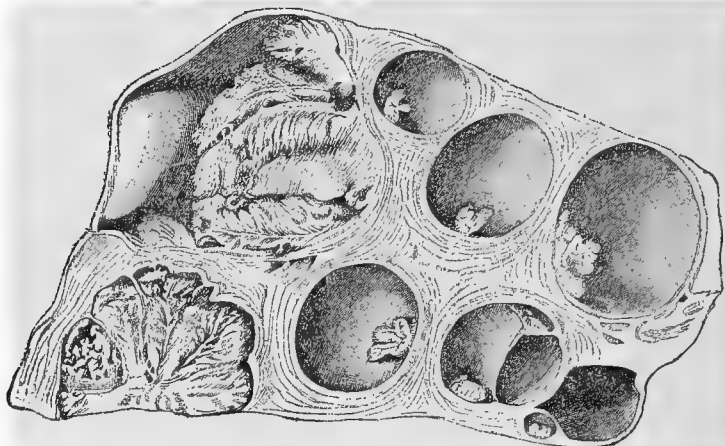
Fig. 303.—Portion of a papillary adenocystoma of the ovary, seen in section. (Drawn from a specimen hardened in chromic acid.) Four-fifths natural size.

In one group of cases polycystic degeneration of the kidneys is encountered during intrauterine life and there are instances in which distention of the cysts had reached such a stage as to interfere with birth. In another group of cases the child is born with well developed polycystic kidneys and dies shortly after birth. In still another group, however, the individual attains adult life. The condition is not common. For example, in 6,500 autopsies at Bellevue Hospital, polycystic degeneration of the kidneys was encountered in four cases only. All of them were in adults. It seems that in certain cases the individual is born with cystic kidneys in which the amount of secreting substance, however, is compatible with life, but that, as time goes on, the gradual distention of the cysts so reacts on the intervening kidney tissue as to cause pressure atrophy. In the Bellevue Hospital cases, the patients, toward the end, passed remarkably small quantities of urine and died with symptoms of uraemia. Histologically, polycystic degeneration of the kidneys may, I think, be classified among the cyst-adenomata.

(c) *Carcinoma and Cystocarcinoma.*

§ 121. The **carcinomata** are *malignant epithelial tumors* characterized by *infiltrative growth* and the *formation* of *metastases.*

They develop:

(1) In skin, mucous membranes and glands, all of which appear previously to be normal.

(2) In skin, mucous membranes, and glands, which have already suffered changes.

(3) In papillary epitheliomata, adenomata and adenocystomata.

(4) From the remains of fœtal epithelial structures, and from epithelial tissues which have been misplaced through disturbances of development, and have already developed into pathological formations.

(5) From the epithelial tissues of the chorionic villi and placenta.

The outstanding characteristic of a carcinoma is represented by **atypical proliferations of epithelium which sooner or later penetrate the bordering tissue.** This phenomenon is usually accompanied by **proliferation**
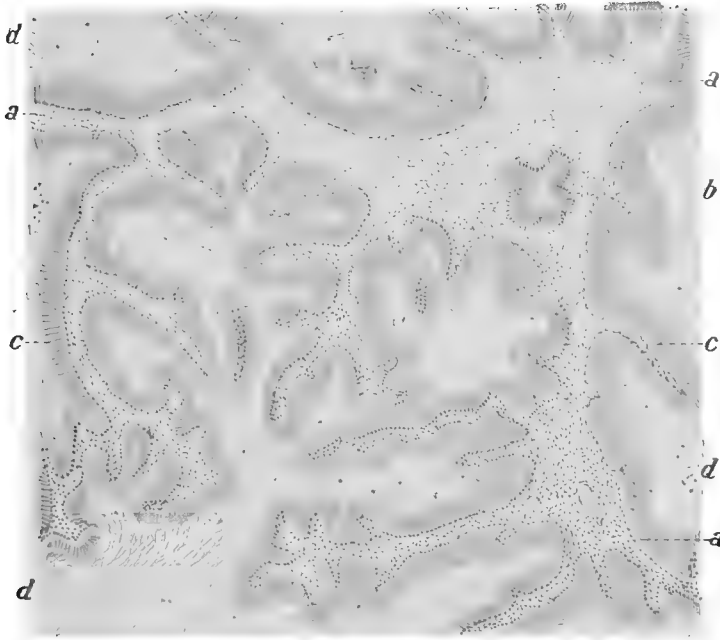
FIG. 304.— Cystoma papilliferum ovarii (Müller's fluid, hæmatoxylin, eosin). *a*, Stroma with papillæ; *b*, gland-tubule with small papillæ; *c*, high cylindrical epithelium; *d*, mucus-containing cells, within the cyst-spaces. × 150.

of connective tissue. The invaded tissue is sooner or later destroyed by the growth. In the stroma of the carcinoma there may occur new-formation of other tissue, for example, bone.

The **cause of the atypical growth of epithelium** is not known; it can only be said that certain conditions favor such growth. For example, *old age* predisposes to the development of carcinomata of the skin, inasmuch as in this period of life the connective tissue of the skin undergoes atrophy and becomes looser in structure, while the epithelium, at least in part, continues to increase (formation of coarser hairs on the nasal septum, lobes of the ears, and in the eyebrows). Likewise carcinomata of mucous membranes and glands usually appear in later years, although they may occur earlier in life, even in childhood.

A further *predisposition to the development* of carcinoma is found in *regenerative processes* following the destruction of surface epithelium and

glandular tissue. These occur most frequently in *old inflammatory processes,* particularly in the mucous membrane of the intestinal tract, gall-bladder, and uterus, and in glands and in the skin. In the stomach the round ulcer may form the starting-point of a cancer. In the first place the regenerative proliferations following injury may form the basis for malignant proliferation. In addition an important rôle is played by *snaring-off and misplacement of epithelial cells into the neighboring altered connective tissue,* as in the healing of ulcers, the growth of epithelium over granulation-tissue, and in tuberculosis, and other chronic infective granulomata, both in the mucous membranes and skin and in glands.

These predisposing factors may exist for a long time without giving rise to cancer. Something else must be added to cause unlimited atypical

FIG. 305.— Papillary adenocystoma of the ovary with myxomatous degeneration of the connective tissue of the papillæ (Müller's fluid, hæmatoxylin). *a,* Fibrous stroma; *b,* papillæ which have undergone myxomatous change; *c,* epithelium. × 80.

proliferation of epithelium, and what this something is is unknown. Whether to be found in a bioplastic stimulus comparable to that of fertilization, or in chemical influences, or in the removal of influences that inhibit and regulate proliferation, cannot be stated.

In recent years the opinion has been advanced that **parasites** cause carcinomatous and sarcomatous proliferations. But the majority of forms described as parasites (protozoa, especially sporozoa, and yeast-fungi) are not parasites at all, but degenerated nuclei and nuclear division-figures, or leucocytes inclosed in tumor-cells, or degeneration-products of such, or of cell-protoplasm, particularly keratohyalin and colloid, or epithelial hyalin and mucin. In the few cases in which true parasites are present in the tissues, this occurrence could well be a secondary infection, in no way to be regarded as a cause of the tumor. *In not a single case has it been proved that parasites are the cause of either carcinoma or sarcoma.*

Certain portions of the intestinal tract—the rectum, the flexures of the colon, the pylorus and cardia of the stomach, the œsophagus, pharynx,

tongue, and gums — are favorite seats for the development of cancer.
Cancer may develop in any portion of the skin, but occurs more frequently
on the lips and nose than on the remaining portions of the face; on the
extremities, more frequently than on the trunk. Of the sexual apparatus
the parts most commonly affected are the mammary gland and cervical
portion of the uterus; less frequently, though relatively often, the ovary,
testicles, body of the uterus, vulva, vagina, and penis. The liver, kidneys,
bladder, trachea, bronchi, lungs and pancreas occupy a middle ground;
while the larynx and gall-bladder are frequently affected.

Cancer usually develops in the form of *nodules, which are not sharply*

FIG. 306.— Papillary systoma or intracanalicular papillary fibroma of the breast, laid open by a
longitudinal incision. One-half natural size.

differentiated from the neighboring tissues; on the mucous membranes
they are not infrequently elevated in the form of *sponge-like, polypoid,*
or *papillary growths*. From the point of origin they spread by **infiltrative
growth** of epithelial prolongations, and the nodules increase in size or
there are formed diffuse superficial thickenings, as in the intestinal wall.
The ovaries, testicles, uterus, kidneys, etc., may be partly or wholly
transformed into carcinomatous tissue. Often the boundaries of the
organ originally affected are overstepped, and the epithelial infiltration ex-
tends into neighboring tissues and organs. Thus, carcinoma of the
mamma may infiltrate neighboring fat, skin, and muscle; carcinoma of the
gums, the maxillary bone; carcinoma of the uterus, the vagina, para-
metrium, bladder, and rectum; cancer of the gall bladder may involve the
liver; one of the thyroid, the trachea; and one arising in the bronchi,
the lungs, etc.

The **formation** of **metastases** may take place through the lymph- or blood-vessels, and is of frequent occurrence by both routes. It leads to the development of secondary nodules in different organs; but it may happen that large lymphatic areas — for example, the lymphatics of the lung — may be dilated by the new-growth, without the formation of circumscribed nodules. The transportation of cancer-cells to the bone-marrow may lead to carcinomatous transformation of the marrow of an entire bone or of several bones. However, it should be noted that probably not every transportation of cancer-cells is followed by the development of a cancer, but that many transplanted cells die.

The **tissue of a carcinoma** is sometimes white and soft, sometimes

FIG. 307.—(Bellevue Hospital.) Rodent ulcer of forehead.

firm and dense; but it is almost always possible to obtain from the cut surface whitish, cloudy fluid called *cancer juice*. Often the cut surface presents a tough, fibrous framework in the meshes of which the softer masses lie; and from which the latter may be squeezed out in the form of plugs or crumb-like masses which consist of **atypically proliferating epithelial cells,** so-called **cancer-cells,** which are found in a *great variety of forms,* and usually show degenerative changes, particularly fatty degeneration. A true *secretion* of cancer cells is usually not found; but cancers occur — particularly in the mucous membranes, ovaries, mammary glands, and thyroid — which produce mucin, pseudo-mucin, or colloid. The amount of secretion may be so abundant as to lead to the formation of *cystocarcinoma.*

Retrograde changes often occur in cancers at an early stage. They are caused by the feeble vitality of the new growth, by circulatory disturbances, which may be due to filling of capillaries and veins by cancer-cells, and by external causes. These changes lead to *destruction of* certain portions of the tumor and the formation of cavities due to lique-

faction of the dead portions, so that, after resorption, the tissues sink in. Such depressed areas are seen particularly in cancer-nodules in the mammary gland, and in secondary nodules in the liver, lungs, and other organs, and are spoken of as *umbilications*.

Retrograde changes often lead to destruction of tumor-tissue, and to the **formation of ulcers.** This occurs particularly in cancers of mucous membranes, but may also take place in carcinomata of the mammary glands and skin. In the latter situation the cancer may take on the appearance of a rodent ulcer. The edge of such ulcers is sometimes elevated and studded with nodules; at other times it is sharply defined and only slightly infiltrated. The base of the ulcer is sometimes fissured and ragged, and covered with necrotic tissue; at other times it is smooth. (Fig. 307.)
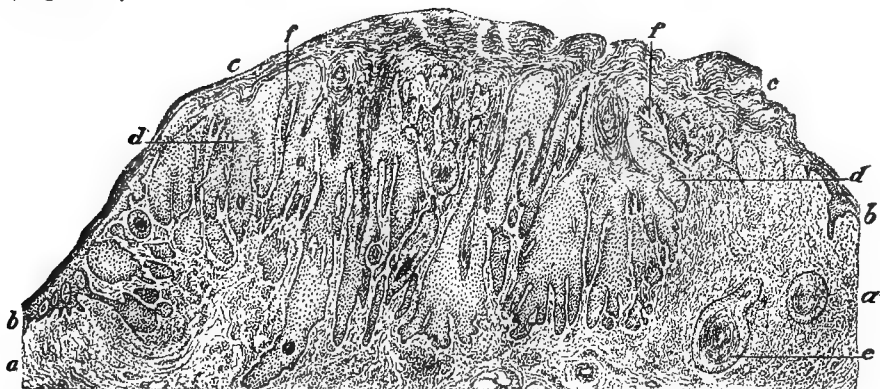
FIG. 308.— Transverse section through a carcinoma of the lip (alcohol, hæmatoxylin, eosin). *a,* Corium, in a state of proliferation; *b,* epithelium; *c,* thickened horny layer; *d,* epithelial plugs extending into the corium; *e,* epithelial plugs with horny pearls, cut obliquely; *f,* enlarged papillæ. × 12.

The view that the **cause of carcinoma and sarcoma is to be found in para-sites** still finds adherents, although the investigations of recent years do not support it. Publications concerning cancer and sarcoma parasites have not been wanting, but in the majority of cases proof has been wanting that the supposed parasites were really living organisms; or, when living organisms (yeasts, rhizopods) have been cultivated from tumors, there has been no positive proof that they stood in causal relation to the neoplasm. The experiments, in particular, of *Sanfelice, Wlaeff, Leopold,* and *Sjöbring* are far from convincing.

It is worthy of note that nearly every author has found a different parasite and has not recognized the parasitic forms described by the others. This speaks against the interpretation of the findings. Moreover, in the majority of the formations described as parasites another interpretation is possible. Some of them are degenerating leucocytes or the remains of such enclosed in cancer-cells; others are vacuoles, hyaline or mucoid products of the cancer-cells, or degenerating nuclei or cell-division figures, or fragments of these. Only rarely is it impossible to give a satisfactory interpretation of the findings, but this fact is not sufficient for ascribing a parasitic nature to the formations. The attempt to compare the "bird's eyes" of von Leyden, or the Plimmer's bodies, to which they correspond, with the parasite found in the root-tumors of cabbage, the *Plasmodiophora brassicæ,* and to regard these root-tumors as analogous to cancer, is, likewise, without justification, since the two diseases have scarcely anything in common. The plasmodiophora multiplies within the plant-cells and distends the latter. Only after the destruction of the affected cells does regenerative proliferation occur in neighboring cells. In cancer there is from the beginning an unlimited and infiltrative growth of tissue-cells.

The natural history and clinical behavior of cancer are not such as to make it probable that it is of parasitic nature. The formation of cancerous tumors as a

result of disturbances of development speaks against this view. The metastases
develop from transported tumor-cells, and cell-inclusions are not necessary to their
formation. The transplantation of cancer and sarcoma into animals of the same
species, and the implantation-cancers occasionally observed after operation, are
the result wholly of the transplantation of living tumor-cells, and cannot be used
as arguments in favor of the parasitic theory. If protozoa are the cause of cancer
we must assume, according to our present knowledge of these parasites, that a
given species can find a suitable soil only in a certain variety of epithelium. Cases
of transmission of cancer from man to man, occasionally cited as evidence, can be
utilized hypothetically in support of the parasitic theory only when the cancer in
the affected individual develops in the same mother-tissue.

Fig. 309.— Beginning development of carcinoma in the vaginal portion of the uterus (alcohol,
Bismarck-brown).   a, Epithelium; b, connective tissue; c, surface epithelium growing into the
deeper tissues; d, dilated glands; e, glandular epithelium growing out in form of plugs; f, cross-
section of a gland, the cylindrical epithelium of which has become converted into stratified
epithelium.   × 45.

§ 122. The **development of carcinoma of the skin** takes place most
often from *surface epithelium*, and is characterized by growth of the inter-
papillary portions into the deeper structures in the form of epithelial
plugs (Fig. 308, d) which fill the connective-tissue spaces. The stratum
corneum (c) may undergo hypertrophy along with the cells of the rete
Malpighii, and penetrate into the deeper tissues with the epithelial plugs
(d). The horny cells which get into the deeper tissues may form epi-
thelial pearls (e).

Besides the surface-epithelium, the *epithelium of the hair-follicles* and *sebaceous glands* may take part in the development of cancer; there
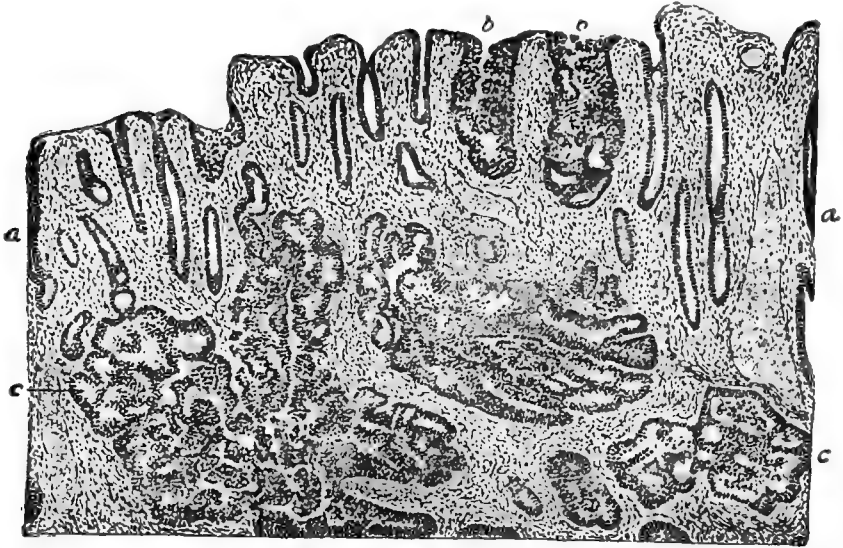
Fig. 310.— Developing adenocarcinoma of the large intestine (Müller's fluid, hæmatoxylin, eosin). *a*, Mucosa with unchanged glands; *b*, glands showing carcinomatous change; *c*, carcinomatous areas in the submucosa. × 100.

are carcinomata of the skin which develop entirely from sebaceous glands, and should be classed with the adenocarcinomata.

The *connective tissue* may remain passive during the ingrowth of epithelium, but sooner or later (Fig. 308, *a*), the papillæ develop into long,
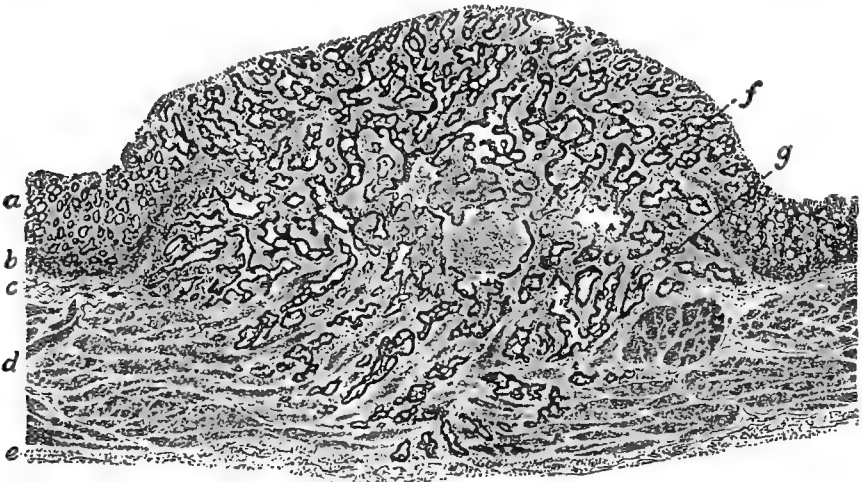
Fig. 311.—Adenocarcinoma of stomach in process of development (formalin, alcohol, hæmatoxylin, eosin). *a*, Mucosa; *b*, muscularis mucosæ; *c*, submucosa; *d*, muscularis; *e*, serosa; *f*, *g*, adenocarcinoma. × 15.

branched formations (*f*). In the proliferating connective tissue there are often found, in association with *fibroblasts, leucocytes* and *lymphocytes.* They become especially numerous in the event of tissue-destruction, and in such circumstances the proliferation of connective tissue acquires the character of granulation tissue.

The **origin of carcinomata from mucous membranes covered with squamous epithelium** may be the same as that of cancer of the skin— that is, it is introduced by *proliferation of surface epithelium* (Fig. 309, *a*, *c*). If *glands* are present they may *take part in the development of the cancer.* It is a remarkable fact that in the formation of such a tumor, glands with cylindrical epithelium may furnish epithelial products which
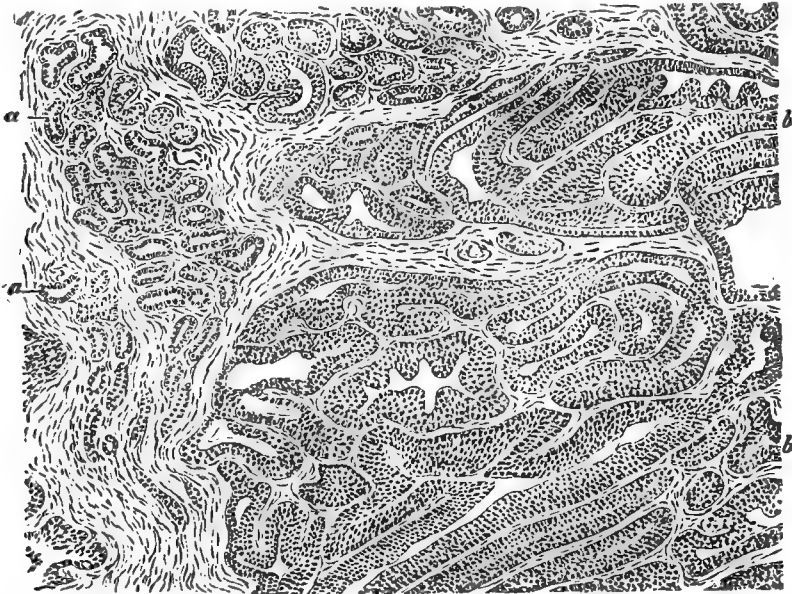
FIG. 312.— Developing cystocarcinoma of mamma (alcohol, hæmatoxylin). Tumor of the size of a bean. *a*, Normal gland-tissue; *b*, proliferating gland- tissue. × 100.

correspond with those of the surface-epithelium. The epithelial pro-liferation may at first be intracanalicular and lead to diffuse thickening and stratification of the epithelium (Fig. ———), or to the formation of ex-crescences (*e*). Later, the proliferating epithelium beaks into the con-nective tissue. The connective tissue behaves in the same manner as in cancer of the skin.

The **cylindrical-cell carcinomata of mucous membranes** arise in the intestine from the *tubular glands* or from the *crypts,* the epithelium of which undergoes proliferation, and becomes stratified, while the glands dilate (Fig. 310, *b*). Later, the glands become changed into branching, atypical structures (*c*), which possess epithelium arranged in layers, and which grow into neighboring tissues.

In the stomach the glands change their character (Fig. 311, *f*), and through continued growth infiltrate the submucosa (*g*), the muscularis (*d*), and the serosa (*e*).

The epithelium of the newly-formed glands stains more deeply with nuclear stains than normal epithelium.

The connective tissue, as in *cancer* of the skin, sooner or later proliferates, and in connection with this there may occur emigration of leucocytes and lymphocytes.

The **development of cancer in glands** — for example, in the mammary gland — likewise begins with *epithelial proliferation*, as the result of which the glands (Fig. 312, *a*) become widened and altered in form (*b*), while their lining epithelium becomes stratified (*b*). With breaking through of epithelium into neighboring tissue spaces, infiltration is begun.
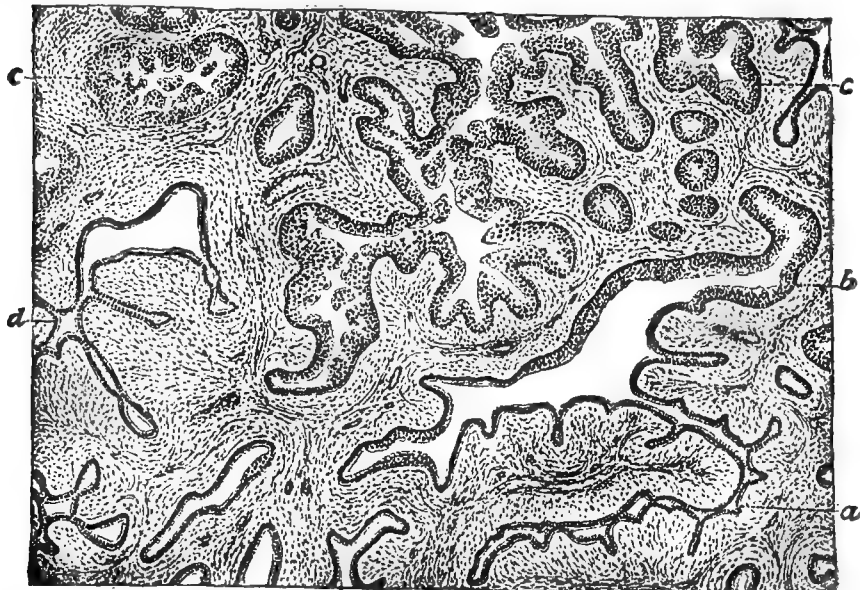
Fig. 313.— Tubular adenoma of mamma showing a beginning transition to carcinoma (formalin, hæmatoxylin). *a*, Branching gland-tubules with simple epithelium; the pericanalicular connective tissue is proliferating and very cellular; *b, c*, gland-tubules, the epithelium of which is partly simple, partly stratified. × 100.

According to the structure of the gland in which the cancer arises, and to the variety of the cancer itself, varying microscopic pictures are produced.

The *connective tissue* of the gland through proliferation takes part in building up the tumor; in the early stages of development such proliferation may be slight or wanting.

The **development of carcinoma in an adenoma** or fibro-adenoma (Fig. 313, *a*) is likewise initiated by change in the character of the cells and by *more active proliferation of the epithelium*, in that simple epithelium becomes stratified (*b, c*). The ingrowth of epithelium into the connective tissue, which often occurs at a late stage, is a further sign of malignancy — that is, of carcinomatous transformation.

The **development of carcinoma from papillary epitheliomata** takes place in the same manner as from the skin and mucous membranes; and is characterized by the infiltration of epithelium into the basement-tissue on which the epithelioma rests.

The **development of carcinoma from transplanted or misplaced epithelium or from remains of fœtal structures** proceeds in the same manner as that of carcinomata arising in surface or glandular epithelium.

Carcinomatous proliferations of the cell-layer and the syncytium of the chorion, both of which arise from the fœtal ectoderm, may occur in the chorion of young ova or in the placenta of older embryos, and in atypical cases are characterized by a mixture of the two forms of cells (Fig. 314). They grow into the neighboring uterine tissue, particularly the blood-vessels (c) and through the formation of thrombi may lead to extensive destruction of the tissues of the uterus, and give rise to metastases. Myxomatous degeneration of the chorion or placental villi (hydatid mole) appears to favor the development of such growths.
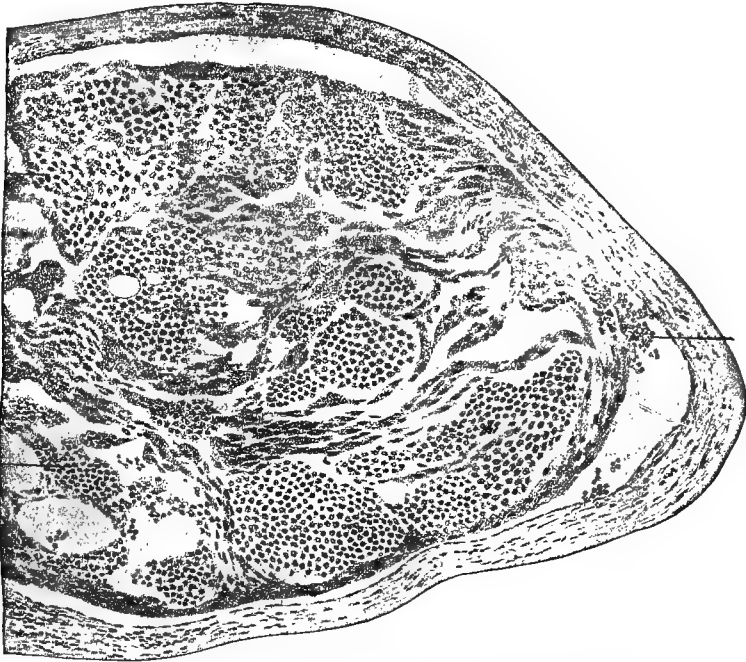
FIG. 314.—Intravascular epithelial plugs of a placental carcinoma.

The **development and growth of carcinoma** have been the object of searching investigation. All writers agree that the developing neoplasm, in so far as its epithelial elements are concerned, grows through its own resources and does not excite neighboring epithelium to proliferation. The neighboring tissue is compressed and infiltrated. On the other hand, differences of opinion exist concerning the beginning of cancer. According to *Hauser, Krompecher, Petersen* and *Colmers,* the development may be unicentric or multicentric, in the latter case starting in several places in the epithelium. *Borrmann* assumes a unicentric origin; in those cases in which the development apparently proceeds from several places he assumes that there is coincident development of several primary cancers.

According to *Hauser, Krompecher,* and *Petersen,* with whom I agree, the development of carcinoma takes place from cells of the superficial epithelium, hair-follicles, glands, and gland-ducts. According to *Borrmann,* a developing carcinoma is a growing cell-complex, which existed as such before it began to grow; it is an isolated embryonal cell-complex. Squamous-cell cancers, although not all of them,

arise from extremely small cell-complexes that lie in the superficial epithelium, and probably become isolated during fœtal life through closure of a furrow or other anomaly of development.

According to the first-named authors, the pathological new-formation has its origin from epithelium or at least takes its point of departure from it. According to *Borrmann* and *Ribbert,* the process begins with inflammatory changes in the connective tissue; in the skin these may be caused by retention and infection of the secretion of the sebaceous glands causing elevation and stretching of the epithelium. As the result of this stretching and accompanying hyperæmia, the included fœtal cell-complex proliferates and grows into the deeper tissues.

The independent proliferations of the fœtal ectoderm are usually designated **chorioepithelioma** (*Marchand*) in accordance with the view that they represent epithelial proliferation. There is no reason for not classing them with the **carcino-**
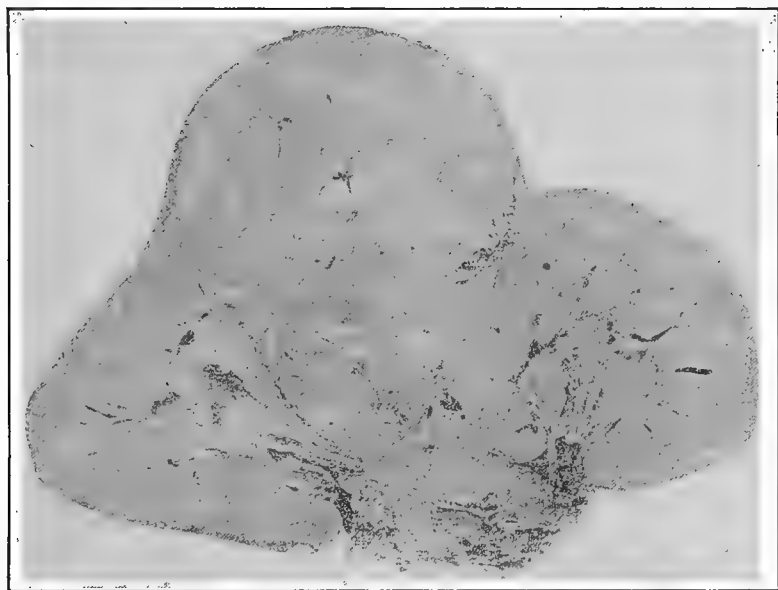
Fig. 315.—(Bellevue Hospital.) Carcinoma of the kidney.

mata, since they are characterized by epithelial proliferation which infiltrates neighboring tissues. The metastasis through the blood-vessels which characterizes the chorionic carcinomata occurs frequently in other carcinomata, for example, carcinomata of the stomach.

To a certain extent the character of the parent tissue is preserved in cancer-cells, but careful examination shows in all cases that there is a certain amount of change both in their morphological and in their physiological character (*anaplasia*). This is shown in changes in the form and structure of the cells, their behavior toward stains, in altered position and arrangement of cells, and in their relations to surrounding tissues.

The traumatic displacement of surface-epithelium in wounds may lead to the formation of so-called **traumatic epithelial cysts** — that is, cysts varying in size from a hemp-seed to that of a nut, which are lined with epithelium, and, in case they arise from the epidermis, contain a pultaceous mass of desquamated epithelium. They occur most frequently after puncture-wounds of the volar surface of the fingers and in the hollow of the hand.

§ 123. The **structure of a carcinoma** is determined by its origin. The manner in which the epithelium proliferates and the associated pro-

liferation of connective tissue make it possible to distinguish a **connective-tissue stroma** which contains the blood-vessels, and **nests** and **strands** of cells—the so-called **cancer-plugs**—which are imbedded in the stroma. If the cancer grows into tissue having a special structure, the stroma may thus be provided with muscle-fibres, bone trabeculæ, unchanged glandular tissue, etc.; but these tissues usually die after a time. In general, carcinoma possesses an **alveolar structure,** at times suggesting an imperfectly developed acinous gland, at other times a tubular gland, so that it is possible to distinguish *acinous* and *tubular* types. When the cell-plugs are solid the growth may be called **carcinoma solidum** or merely **carci-**
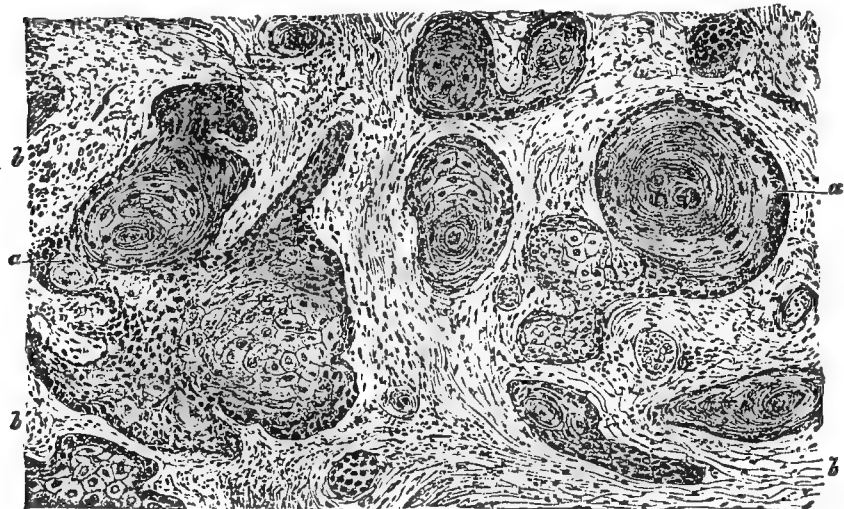
FIG. 316.— Horny cancer of the tongue (Müller's fluid, hæmatoxylin, eosin). *a*, Epithelial plugs with epithelial pearls; *b*, stroma. × 100.

noma. The presence of a lumen in the cell-plugs gives to the growth an appearance resembling the adenomata, and warrants the designation **carcinoma adenomatosum** or **adenocarcinoma.**

The **type of carcinoma** is to a degree *dependent on the parent-tissue,* and the cells may still show the characteristics of the parent epithelium. Squamous-cell carcinoma may occur wherever there is squamous epithelium, and cylindrical-cell carcinomata in mucous membranes having cylindrical cells. Cornification takes place in carcinomata of the skin, mucoid degeneration in those of mucous membranes, while the formation of colloid occurs in those arising from the thyroid. Departures from this rule are common, in that the epithelial cells may remain at a less highly differentiated stage, so that the type of cell concerned may not be developed to its fullest; or it may happen that the cells lose their original character and take on others. For example, colloid-like substances may be formed in cancers of the skin, mucous may be produced in mammary cancers, or squamous-cell carcinomata may develop in mucous membranes possessing cylindrical epithelium (gall-bladder) or in those having transitional epithelium (pelvis of kidney).

(1) **Squamous-cell cancers** develop in the **skin** and in **mucous membranes covered with squamous cells.** They occur, therefore, in the

external skin, mouth cavity, pharynx, œsophagus, larynx, vaginal portion of the cervix, vagina, and external genitals. In rare cases they may develop in mucous membranes possessing cylindrical epithelium — for example, in the trachea and gall-bladder, or in the remains of foetal structures, such as the branchial clefts, and dermoids.
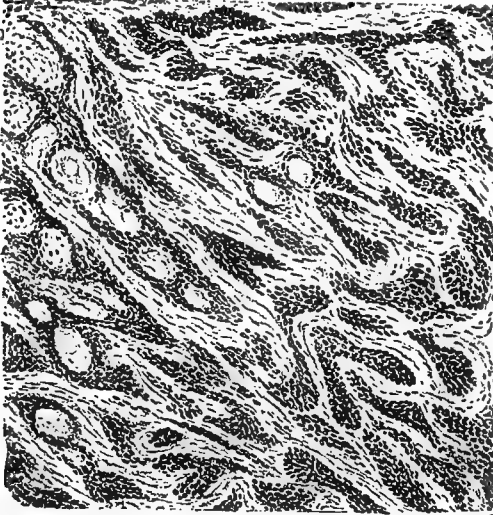
FIG. 317.— Carcinoma of the skin, with delicate cellular network and areas of hyaline connective tissue. (Alcohol, hæmatoxylin.) × 80.

The flat-cell cancer is characterized by the formation of relatively large cell-nests (Fig. 316, *a*) of irregular shape; but often forms small strands of cells. The epithelial cells show the character of stratified squamous epithelium with the formation of prickle-cells, but on account of their multiplication in the tissue-spaces are usually *polymorphous,* and no longer manifest typical characteristics. Often the formation of keratohyalin and cornification takes place in the large epithelial plugs which have penetrated the deeper tissues. The cells which have undergone horny change become arranged in concentric
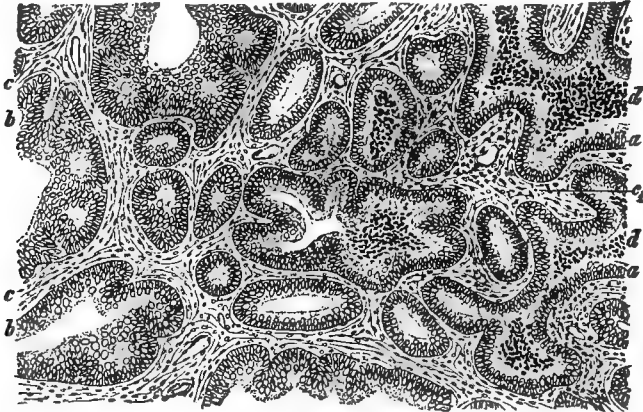
FIG. 318.—Adenocarcinoma recti tubulare (alcohol, alum-carmine). *a, b,* Epithelial gland-tubules; *c, c*₁, stroma; *d,* collections of leucocytes in the gland-tubules. × 65.

laminæ resembling those of an onion (Fig. 316, *a*). Such cell-nests are known as *epithelial pearls* or *horny bodies,* and occasion the designation of *horny cancer.* If, instead of cornification, the central portions of the

cell-nests undergo necrosis and liquefaction, the carcinoma may take on an *adenoma-like* structure.

Besides typical flat-cell cancers there often occur in the skin and in mucous membranes possessing squamous cells, **carcinomata having epithelium persisting at a lower stage of development,** so that the cell-strands remain slender and delicate, and consist of small epithelial cells of different forms (Fig. 317) that do not change into prickle and horny cells. Such cancers are called *basal-cell carcinomata,* since they develop from the layer of basal cells. The cell-cords are usually solid, but through the
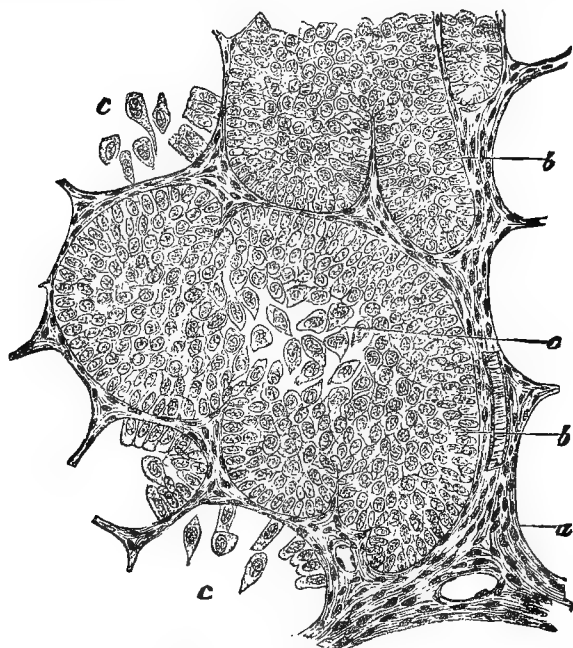
Fig. 319.—Adenocarcinoma fundi uteri. *a,* Stroma; *b,* cancer-plugs; *c,* isolated cancer-cells. × 150.

production of hyaline products in the centre of the cell-masses they may take on an *adenomatous* appearance.

(2) **Cylindrical-cell carcinomata** develop chiefly in mucous membranes possessing cylindrical epithelium — intestines, stomach, respiratory tract, body of the uterus, and gall-bladder, but occur in glands — ovary, mammary gland, liver, etc.— as well as in the cerebral ventricles. Such tumors exhibit, at least in the early stages of development, the character of **carcinoma adenomatosum** or **adenocarcinoma** (Figs. 310, 311, 318), in that they form epithelial structures which consist of tubules lined by simple or stratified epithelium. More active proliferation of the epithelial cells finally leads to the formation of compact cell-nests possessing no lumen (Fig. 319).

The stroma of cylindrical-cell carcinomata is usually poorly developed; and the tumor consequently bears the character of a soft cancer, **carcinoma medullare.** Nevertheless the cancer tissue may in some cases possess a firm consistence.

(3) The **carcinoma simplex** occurs most frequently in glands, but may develop in mucous membranes and skin. The cell-nests are irregularly shaped (Fig. 320); round (Fig. 321), or elongated or fusiform (Fig. 322). These variations occasion the terms **carcinoma acinosum** (Fig.
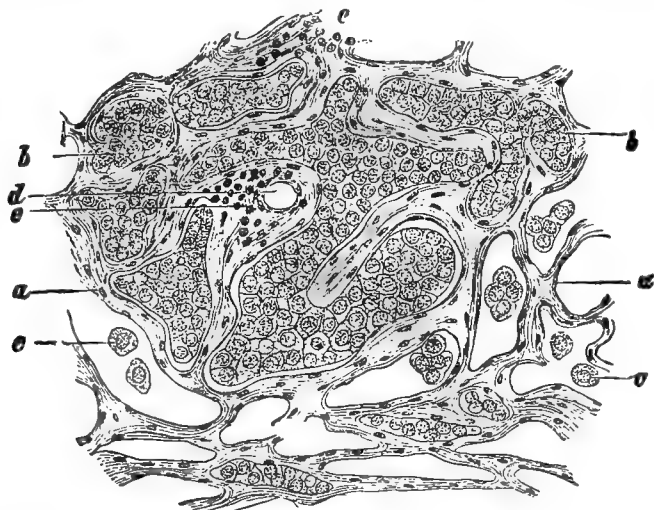
FIG. 320.— Carcinoma simplex mammæ (alcohol, hæmatoxylin). *a*, Stroma; *b*, cancer-plugs; *c*, isolated cancer-cells; *d*, blood-vessels; *e*, small-cell infiltration of the stroma. × 200.

321) and **carcinoma tubulare** (Fig. 322) as distinguishing types of corresponding character. It should be noted, however, that different types may be present in the same tumor (Fig. 323, *e*, *f*, *g*), since the character of the cell-nests depends partly on their manner of growth and partly on
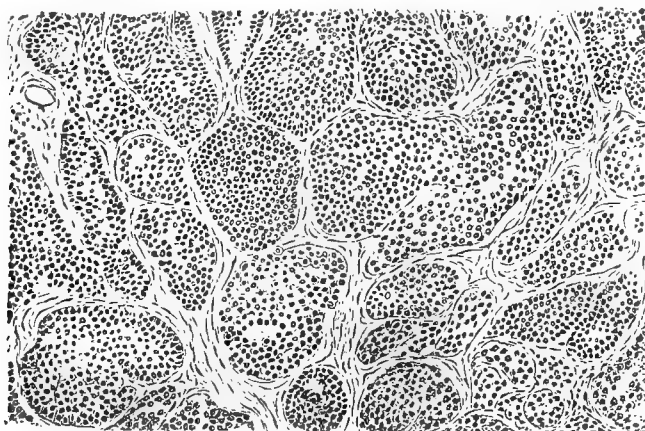
FIG. 321.—Acinous carcinoma of the mammary gland with large nests of cells (Müller's fluid, hæmatoxylin). × 100.

that of the connective-tissue stroma in which they develop. At the seat of origin the cell-nests may have a variety of shapes (*e*); in adipose tissue they are rounded (*f*); in the unyielding connective tissue of the skin they are small and fusiform (*g*).

Abundant development of cell-nests in a delicate connective-tissue stroma leads to the formation of **carcinoma medullare**.   Marked devel-
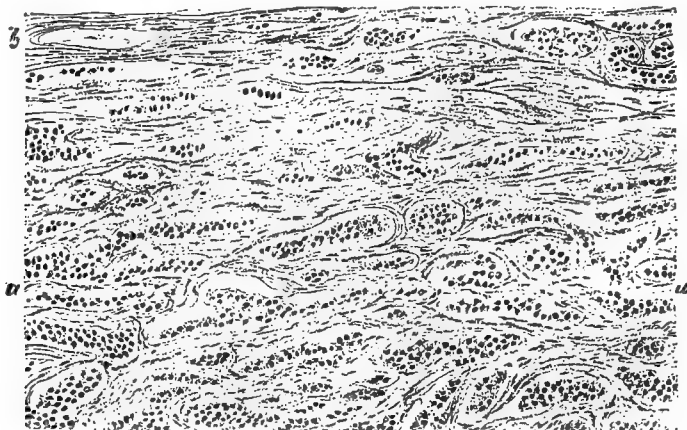
Fig. 322.—Tubular scirrhous cancer of the mammary gland (Müller's fluid, hæmatoxylin). *a*, Area with well-developed elongated nests of cells; *b*, portion of tumor in which the cell-nests have for the greater part disappeared.   × 100.

opment of stroma with the formation of relatively few cancer-cells gives rise to a hard tumor, called **carcinoma durum** or **scirrhus** (Fig. 322).
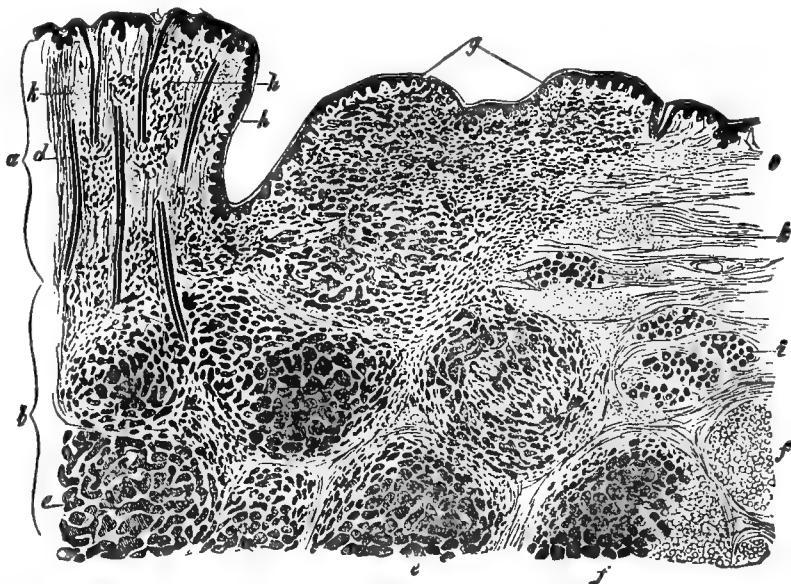
Fig. 323.—Section through a segment of a carcinoma of the breast (alcohol, hæmatoxylin). *a*, Nipple; *b*, tissue of gland; *c*, skin; *d*, gland-ducts; *e*, carcinomatous masses occupying the place of the gland tissue; *f*, carcinomatous infiltration of fat tissue; *g*, portion of skin infiltrated with carcinoma; *h*, nests of cancer-cells in the nipple; *i*, normal gland-lobule; *k*, small-cell infiltration of the connective tissue. Magnified by hand-lens.

The hard variety of cancer owes its origin to the fact that cell-nests are few and small, while the stroma is abundant and hard.   Such tumors

are formed especially when epithelial proliferation infiltrates into hard connective tissue, for example, in the mammary gland and skin, but the
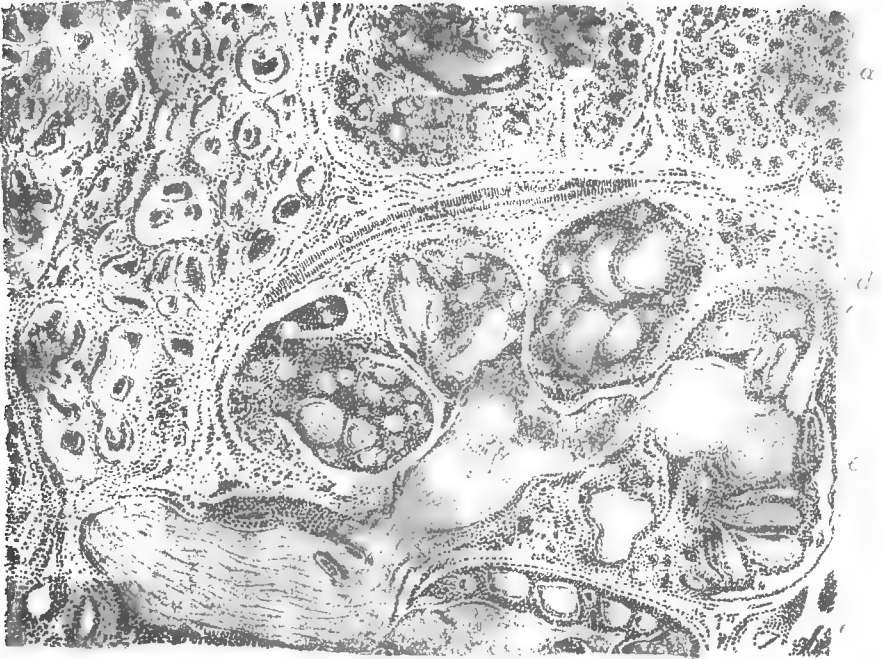
Fig. 324.— Mucoid carcinoma of the mammary gland (Müller's fluid, hæmatoxylin, eosin). *a*, Normal gland tissue; *b*, *c*, early stages of carcinomatous proliferation with beginning formation of mucus; *d*, larger cell-nests with masses of mucus; *e*, *f*, carcinoma tissue showing marked mucous degeneration. × 30.

same characteristics may be exhibited in newly-formed connective tissue. In the course of time a cancer becomes harder by reason of the destruction of its epithelial cells (Fig. 322, *b*), while the connective tissue increases
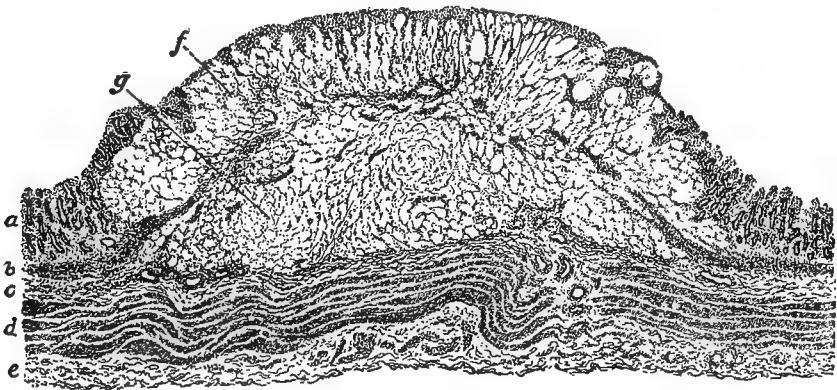
Fig. 325.— Early stages of development of a mucoid carcinoma of stomach, arising in an atrophic mucosa (formalin, alcohol, hæmatoxylin, eosin). *a*, mucosa; *b*, muscularis mucosæ; *c*, submucosa; *d*, muscularis; *e*, serosa; *f*, *g*, mucoid cancer. × 9.

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in amount. An originally **soft cancer may become hard** through **shrinkage of the cancer tissue** with corresponding **induration of the connective tissue.** Carcinomata of the mammary gland, stomach, and intestine often show secondary hardening, and in such tumors cancer-cells may be almost entirely replaced by fibrous overgrowth.

(4) The **chorion-carcinoma** or **malignant chorio-epithelioma** is distinguished from other carcinomata by a mixture of cell-forms (Fig. 314) belonging to the fœtal ectoderm. Such a combination is not everywhere present, and does not occur where single cells or cell-groups penetrate the blood-stream or are transported passively. The conditions favoring development within the blood-vessels are found when fluid and coagulated masses of blood lie between the tumor-cells.

FIG. 326.— Carcinoma mucosum mammæ (alcohol, hæmatoxylin). *a*, Stroma; *b*, cancer-plugs; *c*, alveoli without cancer-cells; *d*, cells containing spherules of mucus. × 200.

(5) **Cancers characterized by peculiar secondary changes** arise through the formation of special products by the cancer cells, or through metamorphoses of the same, or through changes in the stroma.
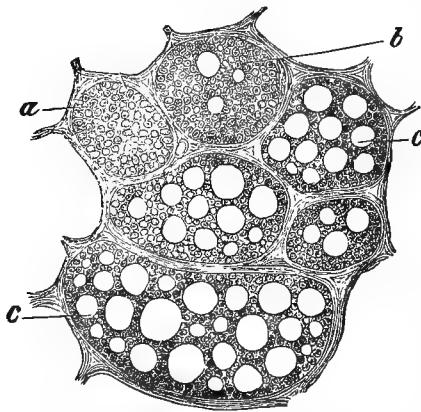
FIG. 327.— Carcinoma with hyaline drops within the cell-nests (Carcinoma cylindromatosum). *a*, Cell-nest without; *b*, cell-nest with a few hyaline spherules; *c*, cells which have been reduced to strands arranged in a network, as the result of the formation of numerous hyaline spherules. × 150.

Mucoid or gelatinous cancer — carcinoma mucosum (*C. gelatinosum, C. colloides*) — is that form of carcinoma in which the epithelial cells produce mucus (mucin or pseudomucin) or a colloid-like gelatinous substance. Such production of mucus occurs particularly in cancers of the intestine, stomach (Fig. 325), and mammary gland (Fig. 324); and may be manifest in the earliest stages of the development of the tumor (Figs. 324, *b, c;* 325, *f, g*), so that the mucoid products of the cells collect in the centre of the cell-nests after the manner of a gland-secretion. Later the border of cells surrounding the mucoid material is broken through, the cells pushed aside, separated from the underlying structures, and crowded toward the centre of the mucus-containing alveolus (Fig. 324, *d, e, f*). Ultimately, the epithelial cells are wholly destroyed.

In intestinal cancers the formation of mucin takes place in goblet-cells, which are similar to the goblet-cells occurring in normal conditions. In cancer of the breast the mucus appears in the form of droplets within the cancer-cells (Fig. 326, d), and becomes free by escaping from the cell, or through destruction of the cell itself.

Through the development of mucoid or colloid-like masses in the cancer-cell nests, the latter may become studded with hyaline drops, and acquire a mesh-like appearance (Fig. 327). Such formations were formerly designated *cylindromata*. Should it be thought desirable to retain this nomenclature, such a tumor might be designated *carcinoma cylindromatosum;* but it seems unnecessary to separate these growths from the mucoid and colloid carcinomata.

Fig. 328.— Enlarged hydropic cancer-cells, from a carcinoma of the mammæ (Müller's fluid, Bismarck-brown). *a,* Ordinary cancer-cells; *b,* hydropic cells containing drops of fluid; *c,* swollen nucleus; *d,* swollen nucleolus; *e,* wandering cells. × 300.

When the cancer-cells attain an extraordinarily large size, for example, in flat-cell cancers or in cancers of the breast, the tumor may be termed **carcinoma gigantocellulare.** If the enlargement of the cells is not due to increase in the protoplasm, but to swelling of the cells or to collection
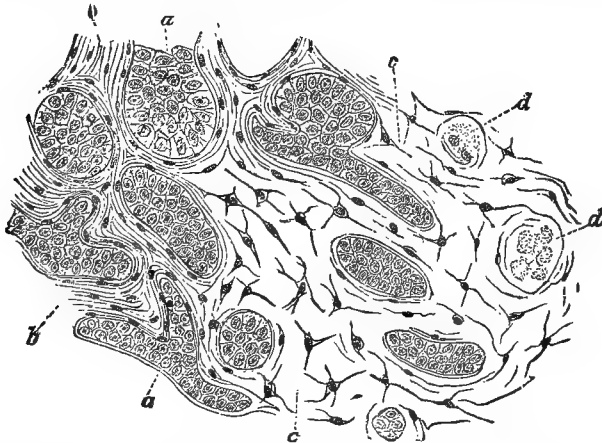
Fig. 329.— Carcinoma myxomatodes ventriculi (Müller's fluid, hæmatoxylin). *a,* Cancer-plugs; *b,* connective-tissue stroma; *c,* stroma of myxomatous tissue; *d,* cancer-cells which have undergone mucous degeneration. × 200.

of fluid in the cells and their nuclei (Fig. 328), the cells are designated *physalides (carcinoma physaliferum).*

Myxomatous degeneration may occur in portions of a cancer, so that the cancer-cells become separated by myxomatous stroma (Fig. 329, *c*). Such growths may be called *carcinoma myxomatosum.*

Hyaline degeneration of the connective tissue occurs in different forms of cancer, but is usually confined to small areas.

Deposits of lime-salts in carcinomata occur as masses similar to those in psammomata. The concretions may form either from the cells or in the connective tissue. They are observed particularly in papillary adenomata and carcinomata of the ovary, and in cancers of the mammary gland. There also occur more extensive calcifications, which may lead to complete **petrifaction**; tumors showing such changes occur in the skin and
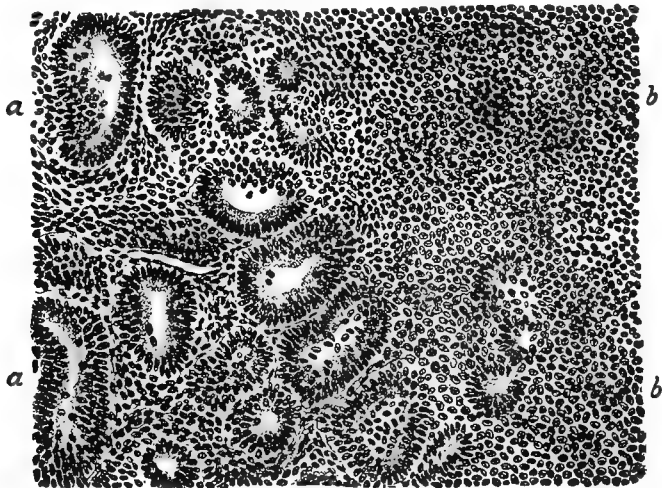
FIG. 330.—Adenosarcoma malignum of the kidney, from a child seven years of age (formalin, hæmatoxylin, eosin). *a*, Tissue with gland-tubules; *b*, sarcoma-like tissue. × 300.

subcutaneous tissues, in the form of sharply defined, hard, rounded nodules. Some of these tumors are to be classed with the carcinomata, others represent calcified adenomata of the sebaceous glands.

If, at the same time with development of the epithelial new-growth, there occurs marked proliferation of the connective tissue, leading to the formation of cellular tissue, there arise tumors which may be designated **adenosarcoma** or **sarcocarcinoma.** Typical examples occur in the kidneys (Fig. 330, *a*, *b*), forming medullary tumors, the origin of which is probably to be referred to disturbance of development of the kidney. Such tumors show a varying structure in different parts, at one time of adenomatous or carcinomatous character, at another time sarcomatous. The metastases of such tumors exhibit a similar character.

The tumor of the kidney referred to by Ziegler as **adeno-sarcoma** was carefully studied by Wilms and frequently goes by his name or under the designation of embryoma. It is a composite tumor which occurs most frequently in the kidneys of infants and children, the growths reaching enormous size and frequently metastasizing to distant parts. Most of them are unilateral, but bilateral growths are by no means unknown. The majority occur in children under twelve years of age, but examples have been recorded in adults. In fact, it is safe to say that an overwhelming majority of all tumors of the kidney encountered in individuals under twelve years of age belong in the category of the so-called Wilms' embryoma. They are made up of a mixture of tissues in which cartilage, smooth muscle, osteoid and myxomatous connective tissue are associated with complex arrangements of epithelial cells, the latter presenting a striking histological resemblance to the tubules

of the developing kidney. (Fig. 330.) Unlike the so-called hypernephromata, the composite tumors of the kidney seldom cause hematuria and are recognized, as a rule, by their rapid growth and massive size. Hedren, of Stockholm (Ziegler's Beitr., 1907), was able to collect only 90 cases from the literature and to add five from his own experience. In the past 15 years I have seen five cases in New York City; three from the service of Bellevue Hospital, one from the New York Hospital and one from an independent source. Of these five tumors, attention was directed to one as a result of the microscopic examination of a small nodule removed from the subcutaneous tissues between the scapulæ, subsequent examina-

Fig. 331.—(Bellevue Hospital.) Massive recurrent Wilms' embryoma of left kidney. The tumor, when removed, weighed 37 pounds.

tion of the abdomen revealing a large embryoma of the left kidney. Surgical removal of these growths is sometimes followed by recovery.

Spontaneous healing of carcinomata does not take place, but many of them grow slowly, and many processes within cancers may be interpreted as *local attempts at healing*. In this category belong degenerative processes in the cancer-cells that lead to their death and dissolution, so that in large areas (for example, in cancer of the stomach) there may be found hyperplastic masses of connective tissue, but no cancer-cells. It is probable that in the destruction of the cells pro-teolytic ferments play a rôle. The occurrence of calcification in a cancer depends on previous death of cells. Further, the fact that transported cancer-cells (compare § 125) do not always give rise to daughter-tumors, but frequently die at the place where they lodge, may be interpreted as a healing process.

Various authors (*Becher, Petersen, Schwarz, Orth*) also look on the occurrence of giant-cells in tumors as a process of healing; it would be more correct, how-

ever, to say that in the course of certain retrograde processes giant-cells appear. The cause of the retrogression lies not in the giant-cells; they appear only under certain conditions, and especially when in cancers elements of certain kinds, corni-
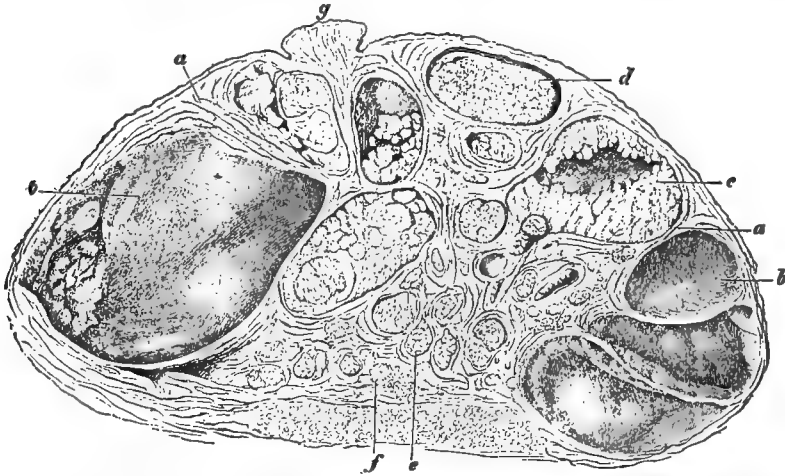
FIG. 332.—Cystocarcinoma papilliferum mammæ. *a*, Stroma; *b*, smooth-walled cysts; *c*, cysts containing papillary proliferations; *d*, cysts entirely filled with papillary proliferations; *e*, small, encysted papillary growths; *f*, adenomatous proliferations; *g*, papilla of the mamma. Reduced about one-third.

fied cells in particular, come in contact with connective tissue. They are foreign-body giant-cells, and their occurrence is to be regarded as secondary to retrograde processes.
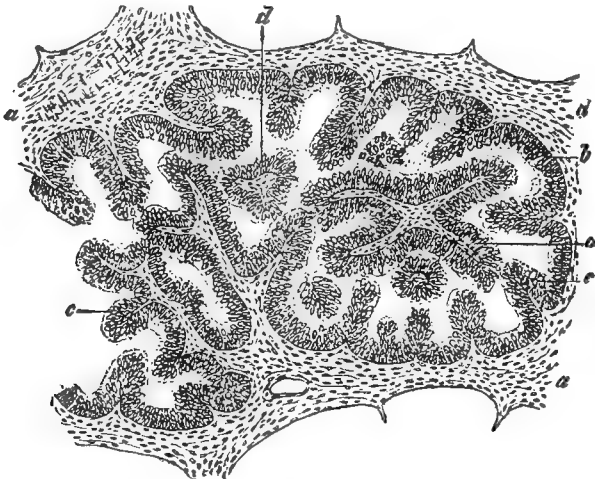
FIG. 333.—Cystocarcinoma papilliferum ovarii (Müller's fluid, hæmatoxylin). *a*, Stroma; *b*, epithelium; *c*, *d*, papillæ. × 72.

§ 124. The **cystocarcinomata** represent a form of tumor which stands in the same relation to cancer as the cystadenomata to the adenomata. The majority of cancers form no demonstrable secretion, but there are certain varieties, particularly in the group of adenocarcinomata, in which the epithelial cells produce mucus or colloid (thyroid); and in

adenocarcinomata of the liver secretion of bile has been observed. In cystocarcinomata the mucous secretion of the epithelium may lead to the formation of large spaces filled with fluid. Cystocarcinomata occur chiefly in the ovary and mammary gland, usually bearing the character of **cystocarcinoma papilliferum** (Fig. 332), in that the cyst-spaces, in certain parts or throughout, are partially (*b, c*) or wholly (*d, e*) filled with papillary proliferations. These excrescences possess a soft, medullary appearance, and when developed in great numbers give to the tumor a marrow-like character.

Both the cyst-wall and the papillary proliferations, which branch in the same manner as those of the papillary cystadenomata, are covered with a thick, stratified layer of epithelium (Fig. 333, *b, c, d;* 334, *c*). The
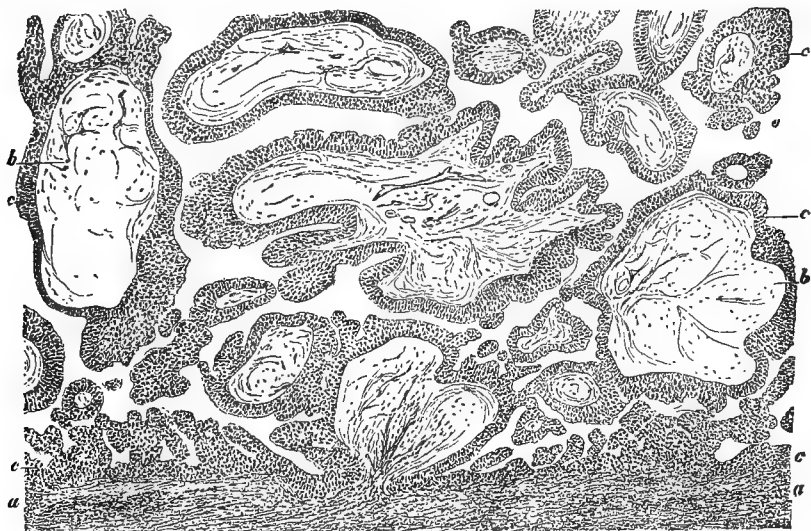
FIG. 334.—Papillary cystocarcinoma of the mamma with papillæ which have undergone myxomatous degeneration (Müller's fluid, hæmatoxylin, eosin). *a*, Dense connective tissue; *b*, myxomatous papillæ; *c*, proliferating epithelium, arranged in several layers. × 73.

papillæ are usually slender (Fig. 333, *c, d*), but through *myxomatous degeneration* of their connective tissue may attain large size (Fig. 334, *b*). Through total *myxomatous degeneration of the connective tissue* of the papillæ the latter may become converted into *mucous cysts* surrounded by epithelium. If at the same time the epithelial layers of neighboring papillæ become confluent, the epithelium finally comes to represent a stroma which incloses balls of mucus.

The metastases of cystocarcinomata may have the character of cauliflower-like, papillary growths. This is particularly the case when ovarian tumors of this nature spread throughout the peritoneal cavity. Other metastases show the characteristics of ordinary carcinomata.

§ 125. **Growth by infiltration and involvement of surrounding tissues** takes place during the early stages of development (§ 122), through penetration of the epithelial elements into the neighboring tissue in the form of connected plugs or cords of cells. Not infrequently there appear in the tissue-spaces single epithelial cells that multiply and form strands or masses of cells. In the growth of a tumor into neighboring

organs, the connective-tissue stroma (Fig. 335, *d*) surrounding the cell-nests breaks into the neighboring tissue (*a*) and replaces it. Such infiltration occurs to the most marked degree in carcinomatous invasion of cartilage (*a*) and bones.

The **formation of metastases,** which takes place more frequently in carcinoma than in any other form of tumor, is the natural result of its infiltrative mode of growth. In the process of infiltration the *cancer-cells break into the lymph-vessels* (Fig. 214), and are carried to the lymph-nodes. In both places there results multiplication of the transported
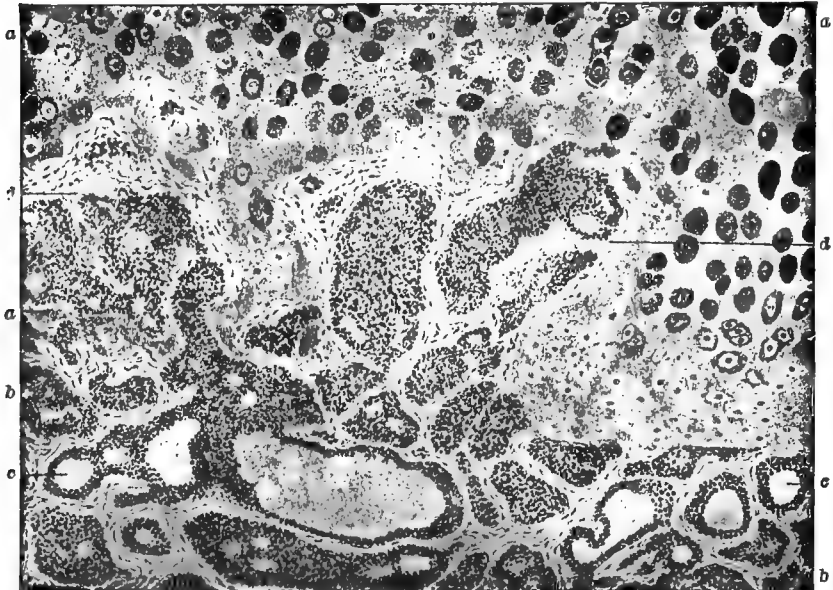
FIG. 335.—Colloid-containing cancer of thyroid infiltrating the thyroid cartilage (alcohol, hæmatoxylin, eosin). *a,* Cartilage; *b,* cancer-tissue; *c,* colloid; *d,* cancer-tissue growing into the cartilage. × 85.

cancer-cells (Figs. 214, *a;* 336, *d*). In lymph-nodes the lymphadenoid tissue becomes replaced by cancer tissue; the lymphocytes vanish, and the connective tissue of the lymph-nodes serves as a framework for the cancer.

The development of cancer in lymph-channels is limited to filling and distention of the lymph-vessels by cancer-cells (Fig. 214) or it may lead to the formation in this situation of daughter-nodules.

The epithelial obstruction of lymph-vessels is often extensive; and through blocking of individual lymph-channels or of the thoracic duct itself, *retrograde metastasis of cancer-cells may be caused.* For example, in cancer of the stomach the lymph-vessels of the mesentery and the thoracic duct, and those of the lungs, or even of the upper extremities, may become the seat of metastatic growths. Through the thoracic duct cancer-cells may be carried into the blood-stream.

The *epithelial proliferation involves blood-vessels* not less frequently than lymphatics; the invasion of veins by cancer-cells is to be regarded as a common phenomenon. In consequence the vessel becomes

filled with cancer-cells, and at a later stage is converted into cancer-tissue, the framework of which is formed through proliferation of constituents of the vessel-wall.

If cancer-cells pass from the thoracic duct or from a vein into the
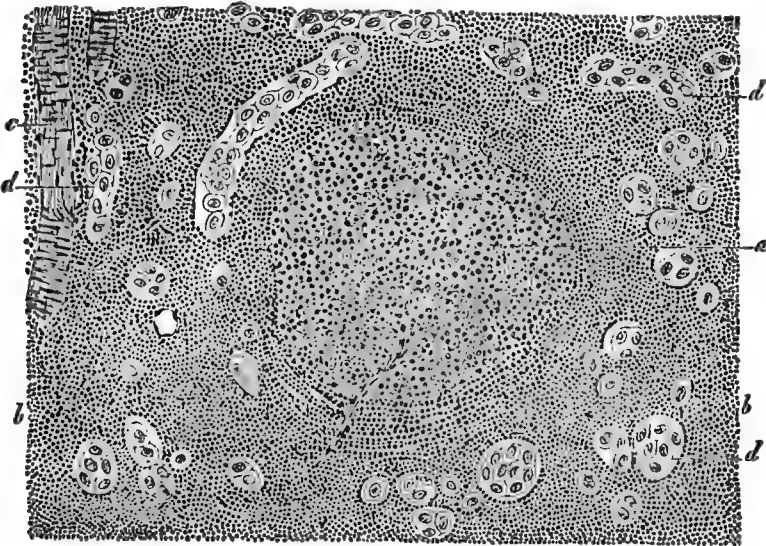
FIG. 336.—Section from an enlarged axillary gland, with beginning development of cancer (alcohol, hæmatoxylin). *a*, Germ-centre of a lymph-node; *b*, lymph-sinuses; *c*, artery; *d*, nests of cancer cells. × 60.

circulation *hæmatogenous metastases* are formed. In carcinoma of the stomach and intestine cancer-cells are often carried through the portal vein into the liver (Fig. 215, *b, c*). The thoracic duct and the systemic veins permit transportation of cancer-cells to the lungs. In fact, the
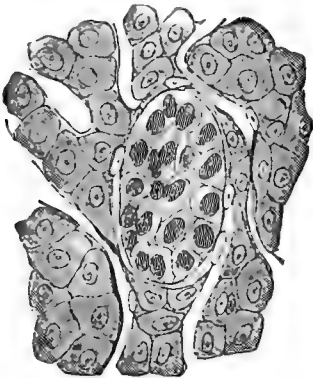
FIG. 337.

FIG. 338.

FIG. 337.—Metastatic collection of young cancer-cells within a liver-capillary, arising from a primary adenocarcinoma of the stomach (alcohol, hæmatoxylin). × 300.
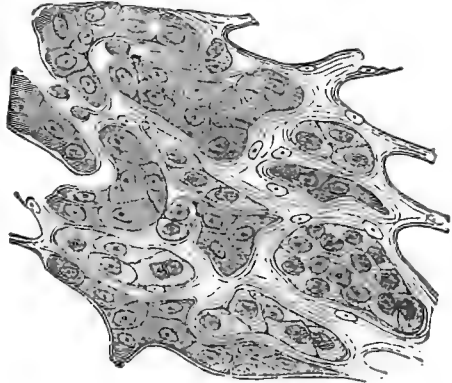
FIG. 338.—Metastatic development of cancer within the liver-capillaries, arising from a primary carcinoma of the pancreas (alcohol, carmine). Both connective tissue and nests of carcinoma cells have developed within the capillaries. × 250.

lungs are frequently the seat of metastases which do not develop into nodules visible macroscopically. Frequently microscopic groups of cancer-cells embedded in thrombi are found. A part of these metastases, through proliferation of the tumor-cells, develops into daughter-nodules, and the lungs may contain numbers of these. The transported cells may die, and there occurs proliferation of connective tissue in the vessel-wall, leading to organization of the thrombus. In other cases the cancer-cells increase within the vessel-lumen without forming large nodules.

When *cancer-cells enter the systemic circulation distribution to various*
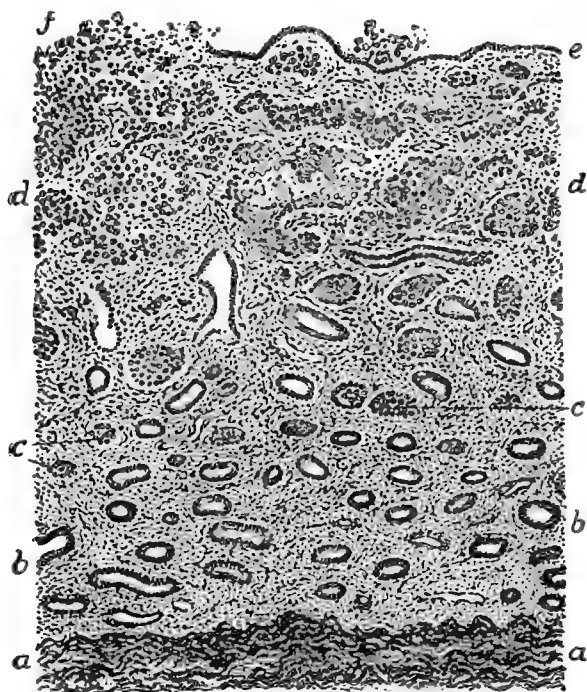
FIG. 339.—Carcinomatous metastases in the upper layer of the uterine mucosa, in universal carcinomatosis following carcinoma of the mamma (formalin, hæmatoxylin and eosin). *a*, Muscularis of the uterus; *b*, normal mucosa; *c*, nests of cancer-cells in the vessels between the uterine glands; *d*, upper layer of the mucosa densely infiltrated with nests of cancer-cells; *e*, uterine epithelium; *f*, ulcerated area. (Blood-clots containing cancer-cells were found in the uterus.) × 100.

organs occurs, although many of the cells die. The favorite seats of secondary development of cancer are the liver, lungs, lymph-nodes and bones. Occasionally development of carcinoma may take place in all the organs of the body; the resulting condition is called *carcinomatosis.*

The *secondary cancer-foci* develop first intravascularly (Figs. 337, 338, and 339, *c*). In the beginning the neighboring tissues are but little changed. Later there occur tissue-degenerations (Fig. 339, *f*) and connective-tissue proliferations (Figs. 338, 340, *c*, *d*), the newly formed connective tissue serving as the stroma for the developing cancer-nodule. The amount of connective tissue varies greatly, and is dependent on the parent-tissue in which the tumor develops and on the variety of cancer. The most marked connective-tissue proliferation occurs in metastases in

bones (Fig. 340), particularly when there is diffuse growth of carcinoma
through the bone. With destruction of old bone the carcinoma may form
an abundant fibrous stroma in which osteoid tissue or new bone may be
produced in large amount. It would appear that certain carcinomata
produce substances that excite marked proliferation of the periosteum and
endosteum.

As has already been mentioned in § 101, **carcinomata may sometimes
be transplanted to individuals of the same** species, and after operations
implantation-carcinomata may develop.

Recurrences after removal of the tumor by operation are common in
cancers, and in advanced cases can scarcely be avoided. They arise
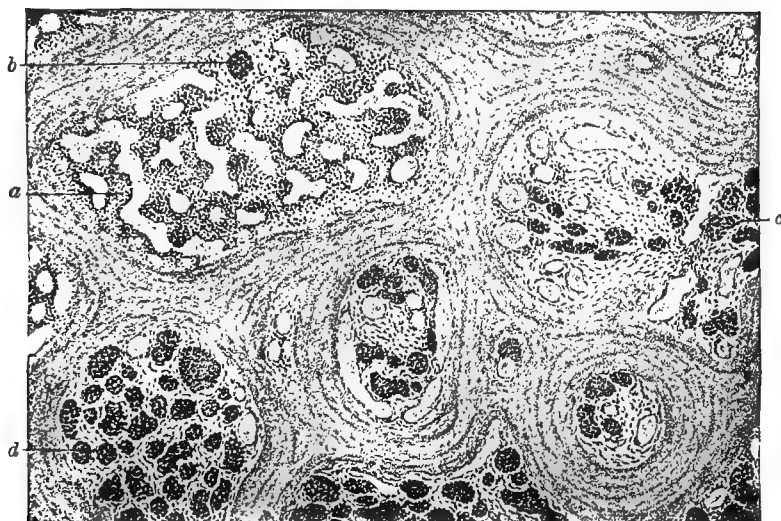
Fig. 340.—Metastatic development of cancer in the diploë of the skull-cap in primary car-
cinoma of the stomach (formalin, hæmatoxylin, eosin). *a*, Marrow-tissue; *b*, nest of cancer-
cells; *c*, proliferated endosteum with nests of cancer-cells; *d*, fully developed area of carcinoma.
× 40.

usually from remains of the primary tumor or from metastases already
present in the body in the immediate neighborhood or in distant organs.
In rare cases the conditions favoring growth of cancer may again arise
in the neighborhood of the scar, so that after several years a *new cancer*
develops.

Recurrences and **metastases of chorionic carcinomata** occasionally grow
extremely rapidly so that in a few days tumors of considerable size may be formed.
The dark-red color shows even to the naked eye that blood is largely concerned in
their make-up, and the microscopic examination demonstrates that the rapid in-
crease in size is in large measure due to the hæmorrhages caused by the development
of the tumor. The epithelial masses may form a relatively small part of the bulk of
the growth.

Chorion carcinomata, that is, the epithelial cell-masses characteristic of these
tumors, have been repeatedly observed *outside the uterus,* in various organs and in
cardiac thrombi without any tumor of the uterus having been demonstrable. This
phenomenon may be explained by the fact that the epithelial cells of the chorion or
of the hydatid mole, that is, of myxomatous chorionic villi, may be transported
through the blood-stream and proliferate without the development of a tumor at
the placental site.

3. The Teratoid Tumors and Cysts.

§ 126. Under the head of **teratoid tumors and cysts** may be grouped those tumor-like growths which are characterized by the fact that the tissue-formations of which they are composed do not occur normally at the ·site in question (*heterotopous growth*), or at least do not normally appear there at the time at which they are found (*heterochronous growth*). Part of the teratoid tumors and cysts classed as **teratomata,** are *composed of a variety of tissues.*

The teratoid tumors and cysts may be divided, according to their structure and origin, into three groups: (1) *The simple teratoid tumors;*
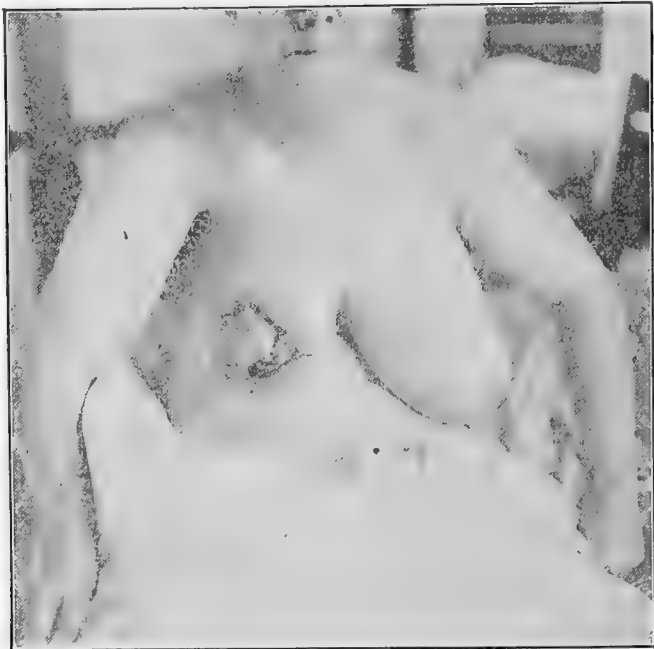
Fig. 341.—(Bellevue Hospital.)   Recurrent carcinoma of the breast.

(2) *the simple teratoid cysts;* (3) *the complex teratomata, which contain tissues derived from all the germ-layers.*

The **heterotopous tissue-growths,** which are classed with the teratoid tumors, may occur in various organs, but are more frequently found in certain regions than in others. Among the common tumors of this class are the chondromata and chondromyxomata of the salivary glands and testicle, osteomata of the muscles, lipomata of the pia mater, adenosarcomata of the kidney containing muscle, and the adrenal tumors found in the kidney. Among those occurring more rarely are the chondromata and osteomata of the skin or of the mammary gland, rhabdomyomata of the testicle, etc.

The occurrence of tissue-formations in regions in which such tissues **are** not normally present can be explained in part by the assumption that

cells or **groups of cells** have not undergone normal differentiation into definite tissue-forms, but **retain the capacity of forming different kinds of tissues.** Nevertheless, in many cases the explanation is to be sought rather in **germinal aberration** or **misplacement of tissue,** in that in early embryonic life cells of one organ find their way into the primordium of another organ, or that, later, tissues in process of development or already formed are displaced from their normal position. The first process can be inferred only from the subsequent appearance of pathological tissue-formations; the latter, on the other hand, may at times be recognized, later on, in the anatomical relations. Thus, in the retrograde changes occurring in hernias of the sacral portion of the spinal cord, adipose and muscle-tissue may find their way into the spinal canal and the arachnoidal sac and grow around the nerves. Arnold observed transposition of fat-tissue, gland-tissue, cartilage, and neuroglia at the lower end of the trunk, in a myelocyst with complete absence of the lumbar, sacral, and coccygeal portions of the spinal column. He also found in a lipomatous teratoma of the frontal region that the intracranial portion of the tumor communicated with the extracranial through a defect in the cranium.

The **teratoid cysts** may be divided into two great groups: the *ectodermal,* and the *entodermal* and *mesodermal epithelial cysts.*

The **ectodermal cysts** vary in size from a pea to that of a man's fist. Their walls present ectodermal characteristics, in that they consist of a smooth connective-tissue membrane, covered with stratified squamous cells — the so-called **epidermoids;** or the cyst walls present all the characteristics of skin — that is, papillæ, sebaceous glands, hair follicles, hairs and sweat-glands, and often subcutaneous fat — the so-called **dermoids** or **dermoid cysts** or **dermatocysts.**

The cyst-contents consist of desquamated horny cells, or of a combination of such cells, fat, and hair.

Epidermoids and *dermoids* are found chiefly in the *skin* and *subcutaneous tissues,* in the form of *growths containing a pultaceous material,* and resemble tumors caused by the retention of secretion in sebaceous glands. They are also found at the sides of the *neck* and in the median line above or below the hyoid bone; in the *thoracic cavity,* particularly in the *mediastinum,* in the *peritoneal cavity* (rarely), *pelvic cellular tissue, coccygeal region,* and in the *raphé of the perineum.* Finally, they appear *within the cranium,* in the dura or hypophysis. Of frequent occurrence are the intracranial formations known as **cholesteatoma** or **pearl tumors.** These growths vary in size from a pea to that of an apple; they form spherical or nodular tumors, having a white satiny surface, and consist of thin, non-nucleated, scale-like cells, arranged in closely crowded laminæ. They are invariably situated at some point on the pia, and at such places the vascular pia is covered with stratified squamous cells, which in the course of years produce the delicate epithelial scales of which the tumor is composed. The neighboring brain tissue and the arachnoid, which may extend over the growth, are not concerned in the formation of the horny scales. In rare cases cholesteatomata contain *sebaceous material* and *fine hairs* in addition to horny scales and cholesterin. In these cases there may be found here and there on the pia *dermal structures,* i. e., skin containing *sebaceous glands* and *hair-follicles,* from which sebaceous material and hairs arise. The simple cholesteatomata may be designated **epidermoids,** those containing hair as **dermoids.** Cholesteatomata occur at the base of the brain, in the neighborhood of the olfactory lobe, tuber

cinereum, corpus callosum, choroid plexus, pons, medulla oblongata (rarely in the spinal cord), and in the cerebellum.

The dermoids and epidermoids probably owe their origin to **transplantation of epithelial germs** to the sites in question. In the epidermoids probably only embryonal epithelial cells are transplanted; in dermoids embryonal dermal tissue is also transplanted. The intracranial cholesteatomata originate probably in early implantation of epidermal cell groups in the pia. Mediastinal dermoids probably depend on disturbances of development of the thymus, which arises from the ectoderm. The dermoids on the sides of the neck arise from remains of the branchial clefts,
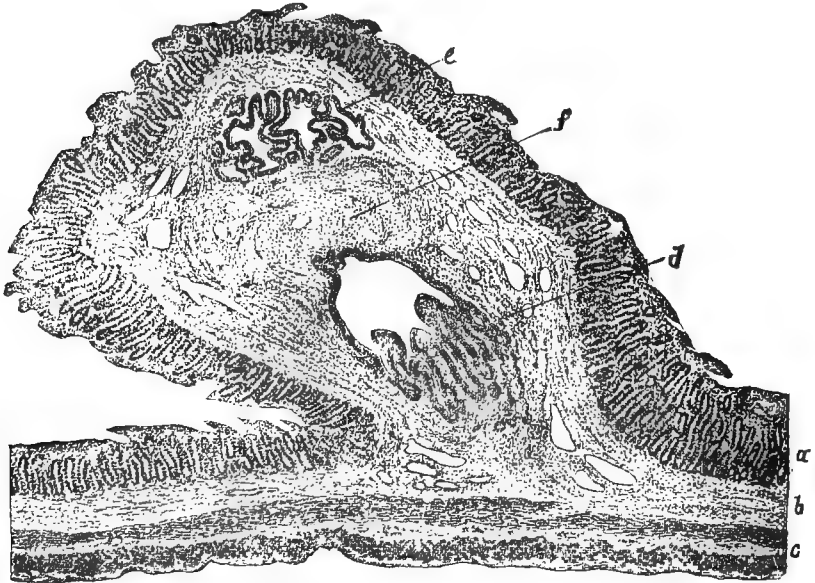
FIG. 342.—Adenoma-like isolation in the submucosa of a portion of the mucous membrane of the small intestine, giving rise to a ridge-like prominence of the mucosa 2 cm. in length (alcohol, hæmatoxylin). From a child six weeks of age. *a, b, c,* Normal intestinal wall; *d, e,* portions of mucosa included within the submucosa; *f,* mucous tissue rich in cells. × 35.

particularly the second; those hanging from the hyoid bone or lying beneath it are probably to be regarded as remains of the ductus thyreoglossus. Dermoids of the pelvic cellular tissue may be explained as arising from epithelial inshoots from the perineum.

Simple **entodermal** and **mesodermal epithelial cysts** are characterized by a lining of cylindrical cells, which are often *ciliated*. They occur most frequently in the broad ligament and tubes. They are also found in other portions of the peritoneal cavity, in the intestine, in the neighborhood of the trachea and bronchi, in the lungs, pleura, neck, tongue, vagina, glandular organs, etc. They form cysts varying in size from a pin-head to that of a man's head.

The occurrence of these cysts may be explained in most cases by the **persistence of fœtal glands or canals** or by **separation through constriction of portions of entodermal or mesodermal epithelial tubes.** In the neck remains of the internal branchial clefts, in the posterior portions of the tongue the remains of the ductus thyreoglossus or of

epithelial buds and glands developing from the same, in the œsophagus and respiratory tract snared-off portions of the intestinal canal or of the air-passages, or remains of the communication between alimentary tract and air-passages, may form the foundation for the development of such cysts. In the broad ligament, uterine wall, and tubes, the cysts arise from remains of the Wolffian duct and the duct of Gärtner; in the tubes, cervix, portio vaginalis, vagina, and hymen they arise from the remains of the latter; in the peritoneal cavity from snared-off portions of the intestine (*enterocysts*), or from portions of the urachus (*urachus-cysts*). Within glands — for example, the liver or kidneys — portions of tubules
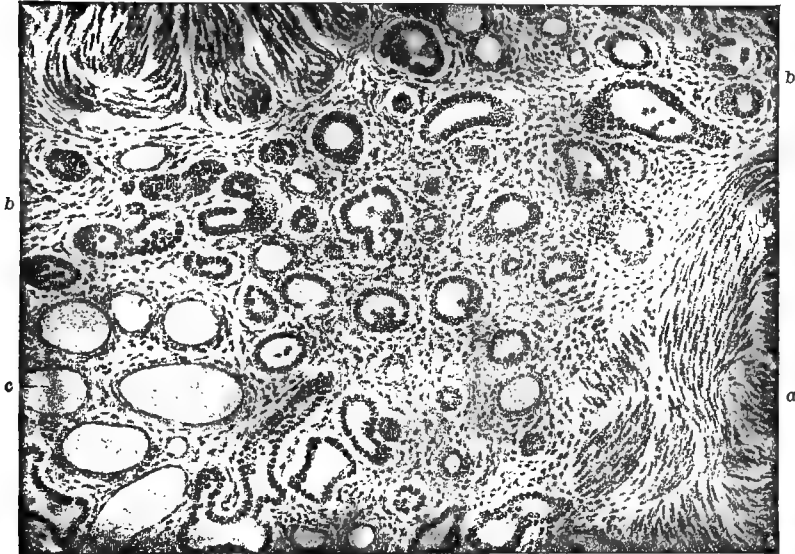
FIG. 343.—Adenoma-like remains of the Wolffian body, within the uterine musculature (formalin, alcohol, hæmatoxylin, eosin). *a*, Muscle tissue; *b*, glandular tissue; *c*, sections of vessels. × 100.

may become constricted during the period of development, and develop into cysts (*adenocysts*).

Cysts located in the central nervous system or its immediate neighborhood — for example, at the lower end of the trunk — may arise from the medullary canal (*myelocysts*), in the latter place also from remains of the hind-gut (*enterocysts*).

The origin of cysts lined with cylindrical epithelium can, as a rule, be determined only from their position and the character of their walls, but in the majority of cases the origin can usually be ascertained beyond doubt. The diagnosis can be made with relative assurance when the misplacement of the separated portion is slight (Fig. 342, *d, e*), and when the formation still shows the character of the mother-tissue.

The significance of ectodermal, entodermal, and mesodermal cysts is dependent on their position, size, and the secondary changes which occur in them. Their size varies from a pin-head to that of a man's head. Among *secondary changes* — aside from *inflammation* — may be mentioned the development of *adenomata* and *carcinomata*. For example, remains of the Wolffian body in the dorsal wall of the uterus near the

angles of the tubes, or in the broad ligament in the inguinal region, may give rise to adenomata, cystadenomata (Fig. 343, *b*), or adenomyomata. *Dermoids* may be the seat of development of a *squamous-cell cancer* (branchiogenic and subcutaneous carcinoma); while from separated portions of the intestinal mucous membrane (Fig. 342) cylindrical-cell carcinomata may take origin. *Cysts, cystadenomata,* and *carcinomata* may
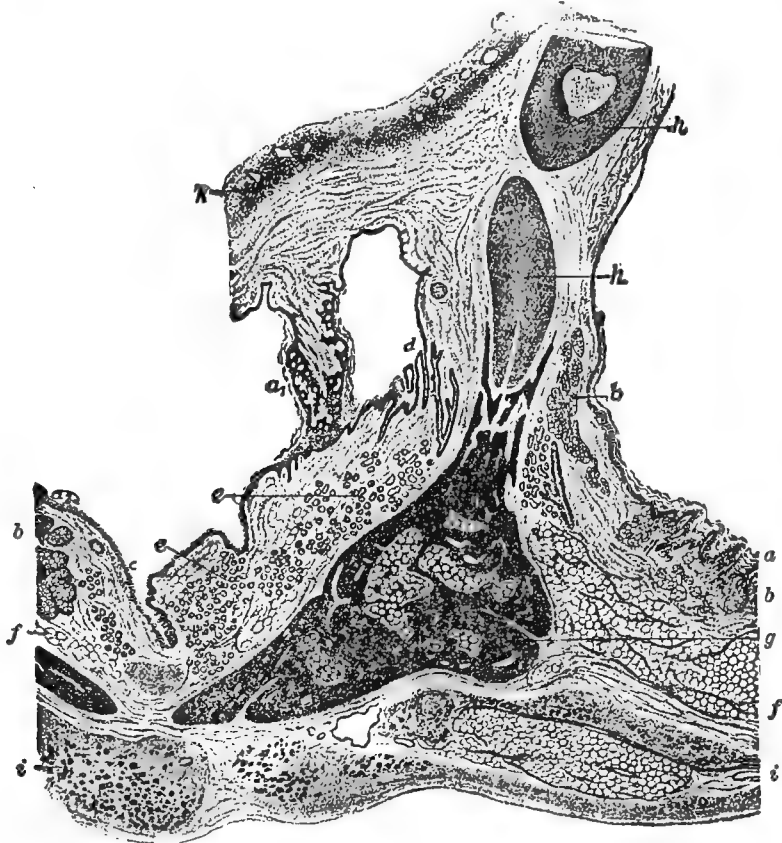
FIG. 344.—Section through a prominence in a mutilocular dermoid (alcohol, nitric acid, hæmatoxylin, eosin). *a, a₁, a₂,* Epidermis; *b,* corium with sebaceous glands; *c,* sinus lined with squamous epithelium; *d,* sinus lined with cylindrical epithelium; *e,* tubular glands; *f,* fat-tissue; *g.* bone; *h,* teeth; *i,* brain-tissue with corpora amylacea; *k,* ovarian tissue. × 5.

develop in the jaw from misplaced portions of the *epithelial primordia of the teeth*.

§ 127. **Complex teratomata** occur most frequently in the sexual glands, in the form of *dermoid cysts* and as *solid tumors associated with multiple cyst-formation.* The first occur particularly in the ovary, the latter in the testicles.

The so-called **dermoid cysts** of the ovary form rather thick-walled cysts, varying in size from a pea to that of a man's head, and are filled with fatty material and hair. At some point in the wall there will be found extending into the cyst-cavity a *villus-like, nodular, flat-*

tened, or *septum-like prominence, covered with hairs and often studded with teeth.* The upper layers of this prominence contain the characteristic structures of the skin (Fig. 344, *a, a₁, a₂, b*), namely, hairfollicles with hairs, sebaceous and sweat-glands; subcutaneous fat is usually present (*f*). In the deeper layers are found tissue-formations, such as cysts and tubes lined with ciliated columnar epithelium (*d*), bone (*g*), cartilage, teeth (*h*), muscle-tissue (heart-muscle [Katsurado]), brain-tissue (*i*), nerves, groups of ganglion-cells, mucous glands, intestinal mucosa, and thyroid tissue, as well as pigmented formations resembling the rudimentary tissues of the eye. The remaining portion of the wall of the dermoid is either covered with cylindrical epithelium or is bare; if hairs are present in this portion, they are the result of secondary implantation, and may be surrounded by granulation-tissue, often by giant-cells. If in association with the cysts containing fat and hairs there are also found cysts filled with serous or mucoid fluid, the latter may be explained as arising through dilatation of spaces which are lined with cylindrical cells. More frequently, however, they represent formations resulting from cystic degeneration of neighboring ovarian follicles or of adenomatous new-growths. The ovary may be entirely destroyed by the dermoid; but remains of its tissue are often present (*k*). In rare cases several dermoids may develop coincidently in one ovary; a doublesided occurrence is seen in about fifteen per cent. of all cases. Ovarian dermoids are observed most frequently in individuals of middle age, but occur in children.

The most characteristic feature of ovarian dermoids is that they contain *elements of all three germ-layers,* and that a certain order in the arrangement of the different elements is observed. The derivatives of the ectoderm and mesoderm, in particular the skin and its appendages, also bone and teeth, and often brain substance, are developed to the greatest extent; while entodermal formations, cylindrical-cell tubules, and mucous glands are developed to a less degree, and lie concealed in the deeper parts of the growth. The structure of the growth as a whole gives the impression of a *rudimentary embryo* with unequal development of ecto- and entodermal tissue; such tumors have been appropriately designated **embryomata** (Wilms).

The **solid teratomata** of the ovary are more rare than dermoid cysts. They form tumors composed of a confused mixture of tissue-formations, e. g., epidermis, epithelial pearls, hairs, sebaceous glands, sweat-glands, tubules, and cysts lined with ciliated epithelium, acinous glands, connective tissue rich in cells, adipose tissue, muscle, cartilage, and bone. In rare cases teeth, intestine, thyroid and brain tissue of rudimentary character may be present.

Since these formations contain *elements of all three germ-layers,* and are distinguishable from the dermoids only through lack of orderly arrangement of the different tissues, and through the more rudimentary development of the individual tissues, they may likewise be classed with the **embryomata.** Because of lack of structural organization approaching that of the human embryo, Wilms has designated these formations *embryoid tumors.*

Since the embryoma contains elements of all three germ-layers, in more or less orderly arrangement, the genesis of such a tumor may be explained by the assumption of *development from an ovum.* Bonnet regards it as probable that in the development of a fertilized ovum, in

25

the early stages of division, a blastomere (or several) may be delayed in division and later give rise to an independent formation containing elements of all germ-layers, or that (Marchand) a fertilized polar body finds its way between the blastomeres of a developing ovum, and later develops within the embryo.   The first assumption seems more probable, and the embryomata of the ovary may consequently be regarded as *rudimentary unioval twin malformations* (§ 128), which are to be placed in the same category with the fœtal inclusions of other organs.   That the ovaries
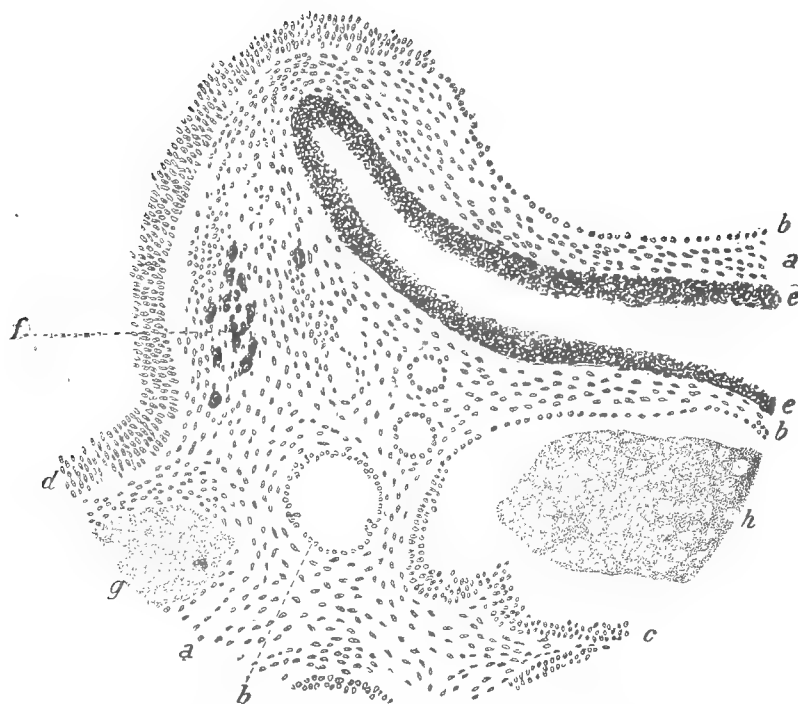
Fig. 345.—Congenital adenocystoma (teratoma) of the testicle with pigmentation and formation of cartilage (Müller's fluid, hæmatoxylin). *a,* Connective-tissue stroma; *b,* simple cubical epithelium; *c,* stratified cylindrical epithelium; *d,* stratified ciliated cylindrical epithelium; *e,* pigmented epithelium lining gland-tubule; *f,* pigmented connective-tissue cells; *g,* cartilage in connective tissue; *h,* cartilage lying in a gland-tubule. (Section taken from tumor pictured in Fig. 300.) × 100.

(and testicles) form the favorite seats of such growths is probably dependent on the fact that the urogenital primordium in its earliest stage forms relatively such a large part of the embryonal primordium (Bonnet), or that the blastomeres, from which the sexual glands later arise, more easily than others take on special development, that may lead to the formation of a rudimentary twin.

The **teratomata of the testicle** occur most frequently as *adenocystoma, chondroadenoma, chondrosarcoma, adenomyosarcoma, cystosarcoma, cystocarcinoma,* etc.   In some cases the formation of cysts with fluid contents is the most striking feature of the tumor (Fig. 300) ; in other cases cysts are found only in certain parts of the growth ; and in still other

cases the tumor may be solid throughout. These growths may reach the size of a child's head. They may be present at birth, but develop more frequently in adult life, and grow rapidly.

The lining of the cysts is, as a rule, of entodermal character, but may vary in one and the same cyst (Fig. 344). Simple cubical (Fig. 344, *b*) and cylindrical epithelium either with or without cilia, as well as stratified ciliated (*d*) and pigmented epithelium (*e*), may be found.

Ectodermal tissue is present in scanty amount, and is limited to pigmented epithelium or to scattered groups of cells showing cornification; or it may be absent, or, at all events, cannot be demonstrated in tumors of large size. Besides the cysts, mucous glands may be found.

Of the connective-tissue substances, fibrous tissue, myxomatous tissue,
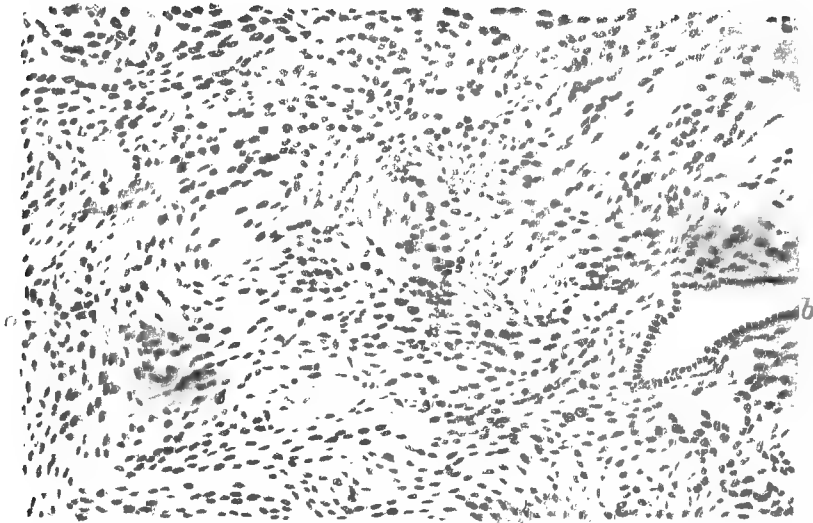
FIG. 346.—Teratoma (adenomyosarcoma) of the testicle (formalin, hæmatoxylin, eosin). *a*, Cellular tissue with bands of muscle; *b*, gland-tubule. × 100.

cartilage (Fig. 345, *g, h*) and occasionally muscle (Fig. 346, *a*), fat tissue, and more rarely bone, are present.

The teratomata of the testicle may contain tissue-formations corresponding in structure to the malignant chorio-epitheliomata, characterized in particular by syncytial formations.

Teratomata of the character of **dermoids,** containing, as in the ovarian dermoids, such structures as skin, brain tissue, cranial and tracheal tissues, and more rarely teeth and structures resembling the eyes, are of rare occurrence in the testicles, but are found both in children and adults.

To what extent the different teratomata of the testicles are to be classed with the **embryomata,** or to what extent they can be explained by the assumption of tissue-implanations at later stages of embryonal development, cannot be stated. When elements of all the germ-layers are present in the tumor, the assumption is justified that the growth belongs to the embryomata or embryoid tumors, and that it has arisen in the same manner as the ovarian dermoids. The occurrence of syncytial formations is in favor of this assumption. The presence of single tissue-

formations — for example, cartilage or muscle — in tumor-formations of a more simple character, may be explained on the ground that such tissues find their way into the testicle during embryonal development.

The *proliferations of chorio-epithelial character* found in teratomata of the testicles are believed to depend on the development of fœtal membranes, and that the myxomatous tissues present in such tumors represent the chorionic stroma. According to *Marchand* and *Risel,* they are to be regarded only as products of the fœtal ectoderm having the same histogenetic significance as the other ectodermal structures of the teratoma. It is yet to be determined to what extent corresponding ectodermal formations occur in teratomata or other organs. *Pick* found them in a teratoma of the ovary in a nine-year-old girl. Further, it is to be noted that syncytial formations occur in tumors (angiosarcoma, endothelioma) having nothing to do with fœtal ectoderm. It cannot, therefore, be regarded as positive.y determined that the syncytial formations in teratomata of the testis actually correspond to chorio-epithelioma. *Wlassow* believes that the chorio-epitheliomatous proliferations observed by him in tumors of the testis, and designated *epithelioma syncytiomatodes,* are to be regarded as derivatives of incompletely developed epithelium of embryonal gland tubules.

§ 128. **Complex teratoid cysts** and **solid teratomata** are found, outside the sexual glands, in the same regions as the simple teratoid cysts, but show a predilection for the region of the coccyx. The complex character of the *cysts* is shown by the presence in the wall of cartilage, bone, fat tissue, mucous glands, smooth and striped muscle fibres, nerve-tissue, and tissue of sarcomatous or carcinomatous nature. Dermoid cysts may contain teeth, and ciliated epithelial cysts. The *solid teratomata* occur as *hairy polypi* (nose, throat, and mouth) — tumors covered with hairy skin, and consisting of adipose tissue, muscle fibres, cartilage, bones, teeth, and cysts. Another group consists of *kidney-tumors* which, in addition to tubular glands, inclose sarcomatous tissue, cartilage, fibrous, adipose, and muscle tissue, in rare cases ectodermal tissues. In the *vagina* and *cervix uteri* of children there occur tumors, for the greater part of a racemose character, which, in addition to connective tissue, myxomatous tissue, round and spindle-cell tissue, contain smooth and striped muscle-fibres, and in rare cases cartilage. Finally, there occur tumor-like growths of complicated structure in the *cranium, thorax, abdomen, urinary bladder, neck, lower jaw,* and especially in the region of the *coccyx.* They contain connective tissue, adipose tissue, cartilage, bone, gland tissue, muscle, nerve and brain substance, as well as ectodermal and entodermal cysts. They may inclose rudimentary, or completely formed, or at least easily recognizable, portions of the body.

Both the complex teratoid cysts and the solid teratomata are in many instances to be regarded as **local disturbances of development** characterized by **misplacement** or **separation of tissues by constriction in a single individual** (*monogerminal tissue-implantation, autochthonous teratoma*). The hairy polypi of the throat, the cystic or solid teratomata at the base of the skull or in the hypophysis may be explained by the assumption of misplacement of ectodermal tissue. The presence of cartilage and mucous glands in teratoid cysts of the mediastinum may be explained by the proximity of the trachea. The teratoid mixed tumors of the kidney may be explained by the assumption that, in addition to kidney-tubules and remains of the Wolffian body, products of the mesenchyma arising from the myotome undergo proliferation. The occurrence of squamous-cell formations in such tumors must depend on the fact that ectodermal tissue has found its way into the developing kidney. The presence of

striped muscle-fibres and cartilage in tumors of the vagina and uterus is explainable by implantation of myotome or of sclerotome; although many hold that striped muscle may be formed from unstriped. Wilms believes that the Wolffian duct and its development occasion implantations into the cervix and vagina. In teratomata of the coccygeal region the manifold character of these growths may be explained by the fact that portions of the terminal vertebræ, of the pelvis, and of muscular tissue, as well as remains of the neuroenteric canal, the hind-gut, and the medullary canal, take part in the formation of the tumor. In intracranial teratomata, as well as in simple dermoids, tissue-implantations probably form the basis for the growth. Moreover, there exists the possibility of another mode of origin for these growths — namely, the presence of a **rudimentary twin**, a *bigerminal implantation*. Such an assumption is well founded in those cases in which the teratoma contains fully developed or rudimentary parts of the body, or tissue-formations which cannot be explained by misplacement of the tissue elements of a single fœtus at the spot in question.

CHAPTER IX.

Disturbances of Development and the Resulting Malformations.

I. General Considerations Regarding Disturbances of Development and the Origin of Malformations.

§ 129. After the copulation of sexual nuclei has taken place, the development of the embryo proceeds by progressive division of nuclei and cells, associated with which there arise in orderly manner special cell-complexes and differentiation of the same into tissues and organs. The multiplication of cells, as well as the development of individual cell-groups into organs and parts of the body, depends on intrinsic causes, and is determined by the characteristics which the embryo has received through inheritable paternal or maternal characteristics at the moment of union of the sexual nuclei, which are to be regarded as the carriers. It follows that the characteristics of the species as well as the peculiarities of the individual are predetermined in the germ, and the development of the embryo proceeds under the control of innate moulding forces. Nevertheless, this development is not accomplished without the influence of environment, since the embryo receives its nourishment from the maternal organism, and is exposed to the mechanical influences of its membranes and of the uterus. These influences may operate to modify the development of the fœtus.

In every species of animal, man included, bodily shape and the configuration of organs conform to a *type,* which experience has shown constantly to recur, and which is therefore looked on as normal. If more or less marked departures from this type occur, the condition is designated **congenital malformation.** When departure from the normal is marked, so that the individual is grossly malformed, it is spoken of as a **monster.**

According to usage, the term *malformation* is applied to anomalies in the form of the body as a whole, or to parts of it which present departures from the normal.

A malformation affecting a single individual is known as a **single malformation** or **single monster;** one made up from two individuals is termed a **double malformation** or **double monster.**

Malformations may owe their origin to intrinsic or extrinsic causes.

As **intrinsic causes** may be considered such as exist in the germ. When such a malformation occurs in a family for the first time, it must be regarded as a *primary germ-variation.* This may be explained in one of two ways: either one or both of the sexual nuclei entering into union have been abnormal, or both have been normal, but from their union a variety has arisen which is to be regarded as pathological (cf. § 17). It is also possible that disturbances in the processes of fertilization can give rise to pathological variations.

If a similar malformation has already occurred in the parent, the case may be regarded as one of *inheritance.* If the malformation appearing

is a peculiarity which was not present in the parents, but did show itself in remote ancestors, while wanting in the intermediate links, the phenomenon is designated *atavism*.

Only those malformations are inheritable which originally appeared as primary germ-variations. To such inheritable malformations belong increase in the number of the fingers and toes (polydactylism), malformations of hands and feet, abnormal hairiness, harelip, and certain pathological conditions of the nervous system, for example, multiple fibromata of the peripheral nerves.

Under **extrinsic causes** are to be considered *concussion, pressure, disturbances in the supply of oxygen and nourishment,* and *infections.*

Concussions of the uterus in all probability directly damage the embryo at an early stage. At a later stage the effects of trauma are more often to be sought in tearing loose of the egg and in decidual hæmor-

Fig. 347.—(Bellevue Hospital.)   Polydactylism.

rhages, whereby the nourishment of the embryo is disturbed. It is evident that hæmorrhages from other causes, and changes in the maternal blood, as in infections, and pathological conditions of the uterus itself, have a harmful influence on the developing egg; yet these conditions probably lead more often to death of the fœtus and expulsion of the egg than to the development of a malformation. Infectious diseases in the mother may be transmitted to the fœtus and give rise to characteristic changes in the latter. Abnormal pressure from the uterus or its membranes may be exerted on the embryo, especially when there is deficient amniotic fluid; malformations of the extremities not infrequently show evidences of pressure having been exerted.

In many malformations it appears that **pathological conditions of the amnion** exert a damaging influence on the embryo.

This may be brought about through *adhesions between embryo and amnion,* and by *pressure of the amnion on the embryo.* At the birth of the child adhesions may not infrequently be demonstrated, and their connection with the malformed parts is such as to leave no doubt that they stand in causal relation to the malformation. Such adhesions may give rise to malformations of the cerebral or facial (Fig. 348) portions of the head. Not infrequently extremities are snared off by amniotic bands (Fig. 349), amputated and absorbed.

Some malformations are **typical** — that is, they always appear in the same form; others are **atypical,** so that astonishing anomalies may arise.

Geoffroy St.-Hilaire ("Hist. gén. et partic. des anomalies de l'organization chez l'homme et les animaux," Paris, 1832–37) discards entirely the teaching of a primary abnormality of the germ (*Haller* and *Winslow*), and attributes arrests of development purely to mechanical influences. *Panum* ("Untersuch. über de Entstehung der Missbildungen," Berlin, 1860) agrees with him on the whole, although he admits the possibility of a primary abnormality. He produced malformations in hens' eggs by temperature variations and by varnishing the shells. *Dareste* ("Recherches sur la production artificielle des monstruosités," Paris, 1877) made similar
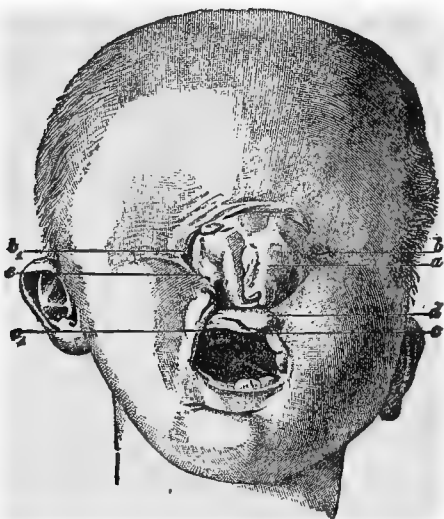
FIG. 348.—Malformation of the face, caused by amniotic adhesion and pressure. Asymmetry of the face. *a,* Malformed nose; *b, b₁,* rudimentary lid-clefts; *c, c₁,* clefts in the upper lip and alveolar process of the upper jaw; *d,* intermaxillary bone with prominent lip; *e,* oblique facial fissure closed by scar tissue so as to form a groove.

FIG. 349.—Hand stunted by amniotic adhesions; ring-finger snared off; middle and index fingers grown together and distorted. Reduced one-sixth.

experiments and produced malformations due to arrested development by keeping the eggs in a vertical position, by varnishing the shells, by raising the temperature above 45° C., and also by irregular warming of the eggs.

L. Gerlach, Fol, Warynsky, Richter, Roux, and *Schultze* have carried on experiments in this line, and have attempted, with partial success, to produce malformations in chicken-embryos through the localized influence of radiant heat, variations of temperature, varnishing of eggs, changes of position, injuries, removal of a portion of the white of the egg, and by agitation. *Roux,* experimenting on frogs' eggs, found that, after destruction of one of the first segmentation-spheres, the other continued to develop and formed the half of an embryo, thus demonstrating that each of the first two segmentation-cells, corresponding in their position to the right and left body-halves, contains within itself material for the corresponding half of the body. But since the body-half which is wanting may later be replaced by subsequent development from the undestroyed half, and a whole structure be produced, each half must also possess the power of producing the other half. According to investigations by *Herlitzka, Driesch, Morgan, Wilson,* and others, the first two or even the first four segmentation-cells in tritons, teleosts, ascidians, and echinoderms possess the power of forming an entire embryo.

Schultze experimented on the eggs of amphibia; these normally always assume such a position that the darkly pigmented protoplasmic substance of lighter specific gravity lies above, the heavier clear protoplasm rich in yolk granules lies below. By placing the eggs in an abnormal position and preventing their return to the normal position malformations may be produced, the degree of malformation standing in direct relation to the size of the angle formed by the line of gravity and the abnormally-placed axis of the egg. By turning the egg through an angle of 180° in the two-cell stage a double monster is regularly produced. The same turning in the eight-cell stage causes complete cessation of development. These disturbances arise from displacements consequent upon sinking of the heavier and rising of the lighter constituents of the egg.

According to the investigations of *O. Hertwig,* the eggs of axolotl, when kept in a 0.7-per-cent. solution of sodium chloride, undergo pathological development, which is confined to the central nervous system in the region of the head and trunk. If frogs' eggs are left before fertilization for one to four days in the uterus of the dead female and are then fertilized, there are formed, besides normal embryos, various malformations due to defective development, for example, spina bifida.

Recent studies have shown that monsters and malformations may be produced by Roentgen irradiation of fertilized ova or of either ova or spermatozoa before fertilization. *Gilman* and *Baetjer* found that the eggs of amblystoma developed abnormally under Roentgen irradiation, the embryos showing no mouths. Chicks developed in exposed eggs presented malformations of the occipital region and extremities and in the distribution of the feathers. *Bardeen* found that in frogs injury to the spermatozoa by Roentgen rays caused the development of monsters from eggs fertilized by such damaged spermatozoa.

§ 130. **Single malformations** may be conveniently divided into five groups.

Among monsters due to defective development may be classed those malformations in which the whole or a part of the body is small and imperfectly developed (*hypoplasia*), and those malformations characterized by absence or stunting (*agenesia* or *aplasia*) of individual organs or parts of the body.

If, in parts or organs which are normally formed by the union of primordia which are originally separated, such union should fail to take place, arrest of development may show itself in the form of *clefts* and *reduplications.* Thus imperfect development of the plates forming the anterior body-wall gives rise to clefts in the median line of the thorax and abdomen; failure of union of the maxillary processes of the first branchial arch with each other or with the nasal process of the frontal bone gives rise to clefts in the face. Defective union of the bilateral portions of the female genital tract results in more or less extensive reduplication of the uterus or vagina.

When the primordia of two organs lie near to each other, these may become united to produce *coalescence* between organs or parts which normally should be separated. For example, the kidneys may be united and the eyes merged into a single organ.

Malformations due to excessive growth are characterized by *abnormal size* or *increase in number* of individual parts. For example, an extremity or a portion of one, as a finger, may reach abnormal size (*partial giant growth*), or the whole body may be involved in abnormal growth (*general giant growth*). Increase in number occurs particularly in the mammary gland, spleen, adrenals, and fingers, *accessory* or *supernumerary organs.*

Among **malformations due to abnormal disposition of organs** are certain anomalies of the organs of the thorax and abdomen. In this class belongs the condition known as *situs transversus* — that is, transposition of the thoracic or abdominal organs, or of both. Various *defects in the*

heart and great vessels may also be classed here, though it should be noted that these are more properly regarded as *arrests of development.*

A fourth group of malformations includes those characterized by **displacement of tissues** and by **persistence of foetal formations,** as already mentioned in §§ 126 and 128.

In the fifth group may be classed those **malformations exhibiting a mixture of sexual characteristics,** known as *true* and *false hermaphroditism.* True hermaphrodites possess both male and female sexual glands; false hermaphrodites are unisexual, but the remainder of the sexual apparatus does not correspond to the sexual gland, or there is simultaneous formation of organs belonging to both the male and female. Some of these malformations are arrests of development; others are to be regarded as cases in which from the original bisexual primordia the organs of both sexes have developed, whereas normally those of one sex undergo retrograde change, and persist only in rudimentary form.

§ 131. **Double monsters** are malformations consisting of two individuals; if both twins are developed (*symmetrical twins*) they are always of the same sex and are united to each other in the same portions of the body; the duplicated portions are usually equally developed, but *unequal* forms occur in which one twin is stunted in its development. *Asymmetrical* forms also occur in which one twin remains rudimentary and is dependent on the other for its nutrition (*parasitic double monster*). Often it is *implanted* in the other (see § 127).

All double monsters arise from **one egg** *and have a common chorion.* In the formation of *symmetrical double monsters* two separate embryonal primordia are probably formed from one germinal vesicle, and in their growth blend with each other to a greater or less extent, but duplication or splitting may occur within a single primordium; this process occurs particularly in anterior reduplications and can be produced experimentally in animals. The genesis of rudimentary *asymmetrical twins* occurs in the manner described in § 127 (Teratomata).

II. The Different Forms of Malformations in Man.

I. Arrests of Development in a Single Individual.

(a) *Arrest of the Development of the Entire Embryonal Primordium.*

§ 132. **Arrest in the development** of **the entire embryo** manifests itself in two ways. If the disturbance is marked, **further development of the embryo is impossible,** and it either dies at once or becomes stunted, and after a certain time perishes. If the disturbance is less severe there develops a normally formed foetus, but it remains small and stunted — that is, a **dwarf is formed.**

A **dead foetus** in the majority of cases is expelled together with its membranes **(abortion).** In other cases the embryo for some cause remains stationary in development, the egg may stay for weeks or even months in the uterus and increase in size, and there arises disproportion between the size of the embryo and the egg. The first changes *after death* are shown in swelling of the central nervous organs, leading to changes in the configuration of the head. Later there occurs infiltration of the tissues with wandering cells, the boundaries of the organs are indistinct, the entire **embryo** becomes cloudy and soft, and finally is **completely dissolved.**

.When a fœtus well advanced in development dies and remains in the maternal organism a **lithopædion** may result. This occurs most frequently in extrauterine pregnancy, in which the embryo lies in the peritoneal cavity, in a tube, or in an ovary. If the fœtus dies at such an advanced stage of development that it cannot be absorbed, it may be carried in the maternal body for years. Not infrequently its form is

FIG. 350.—Lithopædion, entirely inclosed in connective-tissue membranes (removed from abdominal cavity by operation two years after beginning of pregnancy). Extrauterine pregnancy caused by embryo breaking through the uterine portion of a tube into the abdominal cavity. Reduced to one-third.

perfectly preserved (Fig. 350), and the fœtus becomes inclosed in a connective-tissue membrane. In other cases the fœtus, in time, becomes partially converted into a fluid mass, which contains osseous remains, fat, cholesterin, and pigment, and is surrounded by a fibrous capsule. Lime-salts are usually deposited in the newly formed membranes as well as in the portions of the fœtus remaining, and for this reason the fœtus is known as a " stone-child " or " petrified child."

According to the condition of the fœtus there may be distinguished three forms of lithopædion. In the first the mummified fœtus may be shelled out from the calcified membranes. In the second form the fœtus becomes adherent to the membranes at various points which become calcified, while the other portions become mummified. In the third form the fœtus is discharged into the peritoneal cavity, and becomes encrusted with lime-salts.

(b) *Defective Closure of the Cerebrospinal Canal and the Accompanying Malformations of the Nervous System.*

§ 133. **Defective closure of the vertebral canal** leads to malformations. If the defect in the vertebral column is open so that at the bottom of the cleft the bodies of the vertebræ covered by membrane are seen, the malformation is termed *rachischisis.* When, at the site of the defect, there is a protruding sac, the malformation is designated *spina bifida,* or *spina bifida cystica.*

FIG. 351.—Craniorachischisis with total absence of the brain and spinal cord. The base of the skull is covered with ragged membranous masses, the open spinal furrow with a delicate membrane (pia mater). Kypholordotic curvature and shortening of the spinal column. Reduced one-sixth.

In **rachischisis totalis** (Fig. 351) the bodies of the vertebræ form a shallow groove opening posteriorly, usually covered by a thin, transparent membrane ; in rare cases rudiments of the spinal cord are present in the form of whitish bands and lines. In this manner there occurs **total** or **partial amyelia.** The defect involves principally the motor tracts and centres, as well as the columns of Clarke and the lateral cerebellar tract, while the spinal ganglia are developed and may send sensory fibres into the membranous masses of the spinal groove.

The delicate membrane which lines the furrow and covers the dura mater lying beneath it on the bones is the ventral portion of the spinal pia mater. A part of the nerve-roots may have undergone development, arising either from rudiments of the spinal cord or from spinal ganglia.

Partial rachischisis usually involves the sacrolumbar or the upper cervical region, while the intervening portions of the vertebral column are only rarely the seat of malformations. The dorsal surfaces, with the overlying dura and pia mater, of the bodies of the vertebræ whose arches remain rudimentary are covered for the greater part by a mass of **velvety,**

vascular tissue, which contains rudiments of the spinal cord (the *area medullo-vasculosa,* von Recklinghausen), though the amount of this tissue may be small or even wanting. To the outside of this layer, which is not everywhere equally abundant and which diminishes at the sides, there

Fɪɢ. 352.—Spina bifida sacralis. (After Froriep and Förster.) A girl of nineteen years, born with a tumor the size of a pigeon's egg over the upper sacral and lower lumbar regions, which enlarged from the sixth year on, while at the same time club-feet developed.

comes a delicate, transparent, vascular membrane which represents the continuation of the pia mater covered with epithelium; and outside of this, a zone of epidermoidal tissue somewhat thinner than normal skin, and often covered with many hairs (*zona dermatica*), separating the reddened central area from the normal skin.

Spina bifida cystica or **rachicele** occurs in three forms: *myelomeningocele, meningocele,* and *myelocystocele.* According to site there may be distinguished cervical, dorsal, lumbar, lumbosacral, and sacral spina bifida. In general, spina bifida is characterized by the development of a fluctuating tumor, which in most cases is visible (Fig. 352) on the posterior aspect of the spinal column (*spina bifida posterior*); but instances occur in which the sac projects anteriorly (*spina bifida anterior*), and others in which it is so small that it is covered with normal skin and is not visible externally (*spina bifida occulta*).
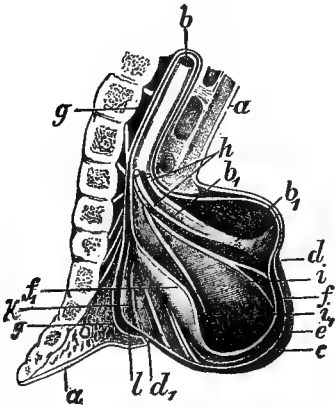
Fɪɢ. 353.—Myelomeningocele sacralis in sagittal section, a little to the left of the median line. (After von Recklinghausen.) *a,* Skin; *b,* *b₁,* spinal cord; *c,* area medullovasculosa; *d,* cranial; *d₁,* caudal polar groove; *e,* arachnoid; *f,* pia, somewhat separated from the arachnoid; *f₁,* portion of pia mater turned over; *g,* dura mater; *h,* recurrent roots of the fourth lumbar nerve; *i,* radix anterior; *i₁,* radix posterior of the fifth lumbar nerve, running free through the arachnoid sac; *k,* sacral nerve-roots between the arachnoid and pia; *l,* filum terminale.

Myelomeningocele appears most frequently as *spina bifida lumbosacralis,* and forms a tumor varying in size from a nut to that of an apple and increasing in size after birth, in the region of the lower lumbar and upper sacral vertebræ. It is covered by smooth or scar-like skin, or may be devoid of skin on its summit and there covered by a reddish, mucosa-like tissue (area medullovasculosa). The portion uncovered by skin may be drawn in, like a scar. In rare cases there may be no external tumor (*spina bifida occulta*), the site of the cleft being indicated by more marked growth of hair or by a depression.

On opening the sac, which is composed of arachnoid (Fig. 353, *e*), and pia (*f, f₁*), while the dura (*g*) does not extend over the dorsal portion of the sac, it may be seen that the lower end of the spinal cord (*b₁*) is drawn outward, and that the cavity of the sac is crossed by nerve-roots (*i, i₁*).

Occasional nerve-roots (h) may also spring from the columns of the cord (b_1) in its course through the sac.

There is, therefore, accumulation of fluid in the meninges, *hydromeningocele,* combined with prolapse of the spinal cord, *myelocele.* At the site of the protrusion the vertebral arches are defective; this defect may reach as far as the hiatus sacralis. Smaller defects may involve only one or two vertebræ.

Dorsal and *cervical meningoceles* are more rare than the lumbosacral. The defect in the vertebral arch is usually confined to one or two vertebræ. The spinal cord is involved in the meningocele, in that portions of it are drawn outward in the form of a band or cone.

Hydromeningocele spinalis arises from hernial protrusion of spinal arachnoid due to localized collection of fluid in the subarachnoid space. It may occur at the upper end of the spinal column in a cleft of the cervical vertebræ, at the same time with hernia of the brain in the occipital region. More frequently, however, it occurs in the sacral region, where protrusion takes place either through a defect in the vertebral arches and bodies or through the hiatus sacralis, or between vertebral arches, or through intervertebral foramina. In the majority of cases the dura takes no part in the formation of the sac, although views differ on this point, and by many writers a dural sac is described. Through progressive accumulation of fluid the sac may attain large size. Small meningoceles may be concealed in the deep tissues.

According to the direction of the hernial protrusion there may be distinguished a *meningocele posterior* and a *meningocele anterior,* the latter taking place through defect in the bodies of the vertebræ.

Myelocystocele or **hydromyelocele** (*syringomyelocele*) takes origin in dilatation of the central canal of the spinal cord, as a result of which a portion of the cord with its connective-tissue envelopes becomes converted into a cystic tumor. The dura is usually wanting over that portion of the sac protruding from the vertebræ.

The wall of these sacs is formed of the inner spinal meninges, but is lined on the interior by cylindrical epithelium, and has at some part of its inner surface an area medullovasculosa — usually on the ventral side, rarely on the dorsal. The roots, if they are still preserved, spring from the ventral, rarely from the dorsal outer wall of the sac. The cavity itself is crossed neither by bands nor by nerves.

Myelocystoceles occur, in the majority of cases, in lateral clefts of the vertebral column. They show a tendency to combine *with defects* and *asymmetries of the bodies of the vertebræ,* and therefore with *shortening of the trunk,* which at times affects only the dorsal region, at other times also the lumbar region. Frequently there co-exists exstrophy of the bladder and intestine.

Myelocystoceles usually are covered only by skin, but are sometimes concealed deep in the soft parts. They may be combined with meningocele — **myelocystomeningocele.**

In cases of rachischisis there sometimes occurs **division of the spinal cord into two parts** (*diastematomyelia*), most often in total rachischisis, in which indeed only rudiments of the spinal cord are indicated. In partial rachischisis such division is rare, the separated strands of spinal cord are better developed, and the fibrous and bony coverings may, at the beginning or end of the cleft, send septa between them. Cases have occurred in which each cord-half possessed an H-shaped area of gray matter.

In the earliest embryonic period the medullary groove is formed by the development on both sides of the median line of wall-like elevations of the ectoderm which are designated medullary folds. Through the converging growth and union of the latter the medullary groove is closed and formed into the medullary canal. Thereupon the cell-masses (primitive vertebral plates) lying at the sides of the newly formed canal form an envelope about it, which gives rise to a membranous, non-articulated vertebral column. In this, at the beginning of the second month, there arise discrete cartilaginous areas from which, in the course of further development, the vertebral bodies and arches are formed, while between them the intervertebral discs and vertebral ligaments appear. The development of the cartilaginous vertebræ is not completed until the fourth month, and up to this time the dorsal covering of the medullary tube consists of the united portions of the membranous vertebral column. The cartilaginous constituents of the vertebræ are in the course of development replaced by bone.

The *origin of rachischisis* is to be referred to agenesia and hypoplasia of the medullary folds, which should form the medullary groove of the vertebral arches. The agenesia of the spinal cord is also to be dated from the very earliest period.
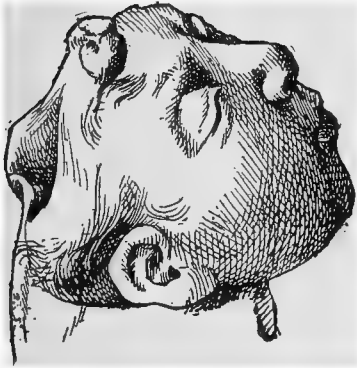
FIG. 354.—Anencephalia et acrania. Reduced one-half.

FIG. 355.—Cranioschisis with Exencephalia.

Whether it is a primary agenesia predetermined in the germ, or whether extrinsic influences, perhaps toxic substances (*Hertwig*), pressure from without, or the inclosure of fœtal membranes, may have secondarily checked development or have destroyed parts already formed, it is difficult to determine; the symmetrical distribution of the arrested development speaks in favor of the former view.

In cases of *spina bifida* with hernial protrusion, *local defects in the bony vertebral column and defective development of the dura mater,* which is usually wanting at the site of the protrusion, are to be regarded as the primary condition. The growth of the sac may be explained as due to congestive and inflammatory transudation, and the residue of inflammatory changes, such as thickenings and membranous adhesions, may often be demonstrated in the pia.

Von Recklinghausen refers the origin of myelocystocele and myelocystomeningocele to deficient growth in the long axis of the vertebral column, characterized anatomically by shortness of the column, absence of vertebrae or parts of vertebrae, separation of wedge-shaped bony pieces from the bodies of the vertebræ, and by unilateral defects in the arches. The neural canal, then, in the course of normal development, becomes too long for the vertebral canal, and in consequence becomes curled or kinked, and there is a tendency to partial protrusion of the medullary tube at the point of sharpest bending. *Marchand* believes that this hypothesis is not applicable to all cases, and *Arnold* is also of the opinion that the causal relations between arrests of development in the muscle-plates and vertebral primordium on the one hand, and those of the medullary canal on the other, are not constant, but that a variety of harmful influences may give rise to one or more

of these anomalies. *Lucksch* emphasizes the effects of pressure as the cause of myeloschisis, but without excluding other causes.

According to *O. Hertwig,* the ordinary spina bifida is an arrest of development depending on partially prevented closure of the blastopore ("Urmundspalte").

§ 134. **Faulty development of the cranium** and associated **disturbances of cerebral development** lead to those malformations k n o w n a s *cranioschisis, acrania, hemicrania, microcephalus, anencephalus, exencephalus, micrencephalus, and cephalocele.*

Acrania and **hemicrania** or **cranioschisis** are the results of agenesia or hypoplasia of the bony and mem-

Fig. 356.—Partial agenesia of the bones of the cranium in anencephalia. *a,* Defect; *b,* squamous portion of the occipital bone; *c,* parietal bone; *d,* frontal bone. Reduced one-fifth.

branous portions of the cranial vault, which arise as primary disturbances of development or as the result of harmful extrinsic influences on the cerebral primordium.

In *acrania* both the bony portion and the skin of the cranial vault (Figs. 354, 356) are wanting, the base of the skull being covered with membranous vascular tissue.

If the defect in the cranial vault is associated with a similar defect in the vertebral arches, there is produced the condition known as **craniora-**

Fig. 357.—Hydrencephalocele occipitalis.

Fig. 358.—Encephalomeningocele nasofrontalis.

chischisis (Fig. 351), in which the spinal column is usually shortened and bent, the head in consequence being drawn sharply backward and the face turned upward. Through bulging of the eyes with deficient development of the forehead, these malformations may resemble frogs (*frog fœtus*).

In *hemicrania* the flat bones of the cranial vault have undergone more or less extensive development (Fig. 356, *b, c, d*) and form a cranial cavity, which is small, in that the flat bones of the vault are elevated but a short distance above the base of the skull. If the bones of the cranium

have undergone imperfect development but unite with one another as under normal conditions, there is produced simple **microcephalus,** which may be present at birth or develop later, as the result of imperfect development of the skull.

Acrania and hemicrania are often associated with **total anencephalus,** the base of the skull being covered by vascular connective tissue with no trace of brain tissue or only rudiments (area cerebrovasculosa).

In other cases the meninges contain, besides cystic cavities and glandlike remnants of the medullary plate, brain-substance, which usually protrudes through the defect in the cranial vault, giving rise to **exencephalus** (Fig. 355). The hernial masses are inclosed by a soft membrane corresponding to the inner meninges, or are covered by skin.

If the cranium presents **partial defects,** portions of the contents may protrude in the form of a sac. Such a condition is known as **hernia cerebri** or **cephalocele** (Figs. 357, 358). The dura mater is wanting over the extracranial portion of the sac.

The size of the protruding sac varies; it may be so small as to be found only after careful examination, or it may be so large as to approach

the brain in volume. If the arachnoid and pia protrude as the result of collection of fluid in the subarachnoid space, the hernia is designated **meningocele.** If at the same time there is a protrusion of brain-substance, it is known as **meningoencephalocele.** A hernia of brain-substance and pia without collection of fluid is an **encephalocele;** if the protruding brain-substance contains a portion of a ventricle filled with fluid, it is designated **hydrencephalocele.**

Cerebral hernias occur chiefly in the occipital region (*hernia occipitalis*), close above the foramen magnum (Fig. 357), and at the root of the nose (*hernia syncipitalis*). In the latter region it may involve the frontal bone (*hernia nasofrontalis*), (Fig. 358), the ethmoid (*hernia naso-ethmoidalis*) or the lachrymal bone (*hernia naso-orbitalis*). More rarely hernias occur on the sides (*hernia lateralis*) or at the base of the skull (*hernia basalis*). The latter may bulge toward the nasopharynx (*hernia sphenopharyngea*), into the orbit (*hernia spheno-orbitalis*), or into the fossa sphenomaxillaris (*hernia sphenomaxillaris*).

In central hernia the brain may be normal or malformed. As a result of marked stunting of development, particularly in the region of the foremost of the three cerebral vesicles, the cerebrum may remain single, while at the same time *deficient separation of the ocular vesicles takes place* (*cyclencephalia* or *cyclocephalia* of St.-Hilaire). In severe grades of this form of maldevelopment only one eye may be formed, lying in the middle of the forehead, or two united eyes may be found in one orbital cavity — (Fig. 359), **cyclopia,** (or **synophthalmus,**) and **arrhinencephalus.** The nose is also stunted (Fig. 359) and forms a cutaneous tag attached above the eye, and devoid of bony foundation (*ethmocephalia*).

When the eyes are separate, yet abnormally close together, the nose may be normal, though small at the root (*cebocephalia*).

In more severe grades of these malformations the ethmoid bone and nasal septum may be wanting, and the upper lip and palate cleft in the

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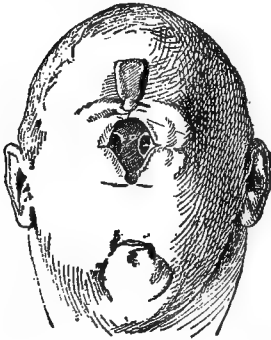
median line, on one or both sides. In lighter grades the forehead is reduced in size and pointed.

In the severe forms the cerebrum consists of a sac, occupying more or less of the cranial cavity and filled with clear fluid; at those points where the sac does not touch the cranial wall the intervening space is filled by fluid distending the subarachnoid space (*h*). In the less marked forms only individual portions of the brain are undeveloped, those parts chiefly affected being the olfactory lobes and nerves, the corpus callosum, a part of the convolutions, etc. The optic thalami are often blended. The chiasm and the optic tract may be absent or present. The corpora quadrigemina (*k*), pons, medulla oblongata, and cerebellum (*l*) are usually unaffected.

The spinal cord and brain arise from the medullary canal. In that portion that is to become the brain, the neural canal changes very early into three vesicles. The most anterior of these, the forebrain, throws out from its lateral portions the primary optic vesicles, while the middle portion grows forward and upward and divides into the *telencephalon* or *forebrain,* and the *diencephalon* or *tweenbrain.* From the former are developed the cerebral hemispheres, corpora striata, corpus callosum, and the fornix. From the tweenbrain are formed the optic thalami and the floor of the third ventricle. The second vesicle or midbrain forms the corpora quadrigemina, while the third vesicle divides into the isthmus, metencephalon, and myelencephalon, from which there are developed the pons, cerebellum, and medulla oblongata.

The cerebral portion of the medullary canal becomes inclosed by the primitive vertebral plates of the head, which form the membranous primitive skull, the basal portions of which become cartilaginous in the second month of foetal life. In the third month the basal cartilage and the membranous vault begin to ossify.

According to *G. St.-Hilaire, Förster,* and *Panum,* acrania and anencephalus are to be referred to abnormal accumulation of fluid in the cerebral vesicles, *hydrocephalus,* occurring before the fourth month. *Dareste* and *Perls* oppose this view, and point out that in acrania the base of the skull is usually bulged inward and not pressed outward. They therefore seek the cause of acrania in pressure exerted on the cranium from without (*Perls*), due to abnormal tightness of the cephalic cap of the amnion, which retards the development of the cranium. *Lebedeff* seeks the cause of acrania is abnormally sharp bending of the body of the embryo, which, he thinks, occurs when the cephalic end of the embryo grows abnormally in the longitudinal axis, or in case the cephalic covering lags behind in its development.

By sharp bending the change of the medullary groove into the medullary canal is thought to be hindered, or the canal after its formation is destroyed. From this could be explained the later absence of the brain, as well as of the membranous and osseous cranial covering. The cystic formations in the membranes lying on the base of the skull are, according to *Lebedeff,* formed from the folds of the medullary plate, which sink into the mesoderm and are snared off.

Hertwig thinks it possible that chemical substances circulating in the blood or secreted from the wall of the uterus may destroy the primordium of the brain.

According to *K.* and *A. Petrén,* the spinal ganglia in anencephalus are always normally developed; on the other hand, the columns of Clarke, the lateral cerebellar tracts, and the bundles of Gowers are either wanting or imperfectly developed. Likewise the pyramidal tracts are wanting, while the anterior-horn ganglion-cells and the anterior roots are developed. *K.* and *A. Petrén,* therefore, regard the malformation as a system-defect in which neurones of the second order are not formed.

(*c*) *The Malformations of the Face and Neck.*

§ 135. The development of the face not infrequently suffers disturbances leading to more or less marked **malformations,** which may appear alone or in association with malformations of the cranium. If the frontal process and the maxillary processes of the first branchial arch remain in a rudimentary state or are destroyed, there persists at the site of the face an

open sinus giving rise to the conditions known as **aprosopia** (*absence of the face*) and **schistoprosopia** (*cleft face*), which may be associated with defective development of the nose and eyes.

More frequently than these large defects are smaller clefts involving the lips, alveolar process of the upper jaw, the upper jaw itself, and the hard and soft palates (Fig. 360), which are designated **cheilo-gnatho-palatoschisis** or "**wolf's jaw.**" This malformation gives rise to a communication between the mouth and the nasal cavity (Fig. 360). The hard palate is cleft in the part bordering on the vomer; the soft palate in the median line. In the alveolar process of the upper jaw the cleft runs between the canine tooth and the outer incisor or between the outer and inner incisors. The malformation may be bilateral or unilateral.

Not infrequently the cleft involves portions of the regions mentioned,
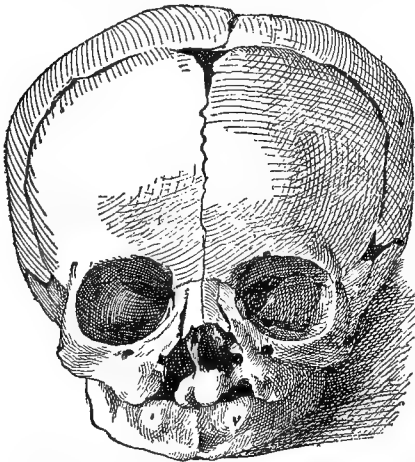
FIG. 360.—Double cheilo-gnathopalatoschisis. (Wolf's jaw.)

FIG. 361.—Agnathia and synotia. (After Guardan.)

as the upper lip (*harelip, labium leporinum*), or the hard or soft palate. The lightest grades of this form of cleft-malformation are represented by a *notch in the lips* or by *bifurcation of the uvula*.

Prosoposchisis or **oblique facial cleft** (Fig. 348) is the designation applied to a cleft running obliquely from the mouth to an orbit. It is usually associated with malformations of the brain. Three forms may be distinguished. The first is a cleft beginning in the upper lip as a harelip, passing into the nasal cavity, thence around the ala nasi toward the orbit, and even beyond the latter. The second form likewise begins in the region of a harelip, but extends outward from the nose toward the orbit. The third form extends from the corner of the mouth, outward through the cheek toward the canthus of the eye, and divides the superior maxillary process externally to the canine tooth. A *transverse cleft of the cheek* also occurs, passing from the corner of the mouth toward the temporal region.

Median facial clefts (*nasal cleft*) run in the median line involving the nose, upper jaw, and also the lower jaw, and may extend as far as the sternum. The tongue may be cleft. The defect may extend even to the frontal bone and brain.

All of the above-mentioned clefts may be confined to small portions of the regions mentioned, and may attain varying depths.

If the development of the inferior maxillary process of the first branchial arch is retarded, the inferior maxilla is imperfectly developed or wanting, and there arise those malformations known as **brachygnathia** or **agnathia** (Fig. 361). The lower portion of the face appears as if cut away; the ears are sometimes brought so close as to touch (*synotia*). Uusually the superior maxillary processes are imperfectly developed; not infrequently the ear is malformed.

Abnormal largeness of the mouth (*macrostomia*), abnormal smallness (*microstomia*) closure (*atresia oris*), and duplication of the mouth (*distomia*) are all rare.

When the embryonic external branchial clefts or internal branchial pockets fail to close, there persist fistulæ opening externally or internally, or closed cysts. The former condition is known as **fistula colli congenita.** The mouths of the external fistulæ are usually found at the side of the neck, more rarely nearer to or in the median line; those of the internal fistulæ open into the pharynx, trachea or larynx. Often the remains of the branchial pockets form diverticula of the last-named organs. The fistulæ are covered with mucous epithelium, sometimes ciliated, arising from the visceral branchial pockets, usually from the second. In rare cases there is a complete branchial fistula with both external and internal openings.

Branchial cysts are sometimes lined with ciliated epithelium and contain fluid; they are called *hydrocele colli congenita*. At other times they possess an epidermoidal covering and inclose epidermoidal cell-masses. Cysts of the neck lying in the median line and reaching to the hyoid bone may develop from remains of the ductus thyreoglossus.

The face and neck are developed in part from a single and in part from paired primordia. The latter are represented in the branchial or visceral arches growing from the lateral portions of the base of the skull ventrally in the primitive throat-wall. The single primordium, designated the frontal process, is a prolongation downward of the base and vault of the cranium, and is, in fact, nothing more than the anterior end of the skull. Between the individual branchial arches there are at a certain period cleft-like depressions known as the branchial pockets.

The frontal process and the first branchial arch form the boundaries of the great primitive mouth-opening, which has a diamond shape. In the course of development the first branchial arch sends out two processes, the shorter of which applies itself to the under surface of the anterior portion of the head and forms the upper jaw, while from the longer one the lower jaw is developed. The frontal process, which forms the anterior boundary, gives rise to a broad prolongation of the forehead, and then pushes on two processes which are known as the lateral nasal processes. By further differentiation of the central portion of the frontal process proper, the septum narium is formed, which by means of two spurs, the inner nasal processes, produces the borders of the external nasal opening and the nasal furrow. The lateral nasal processes are the lateral portions of the skull, and later develop within themselves the ethmoid labyrinth, the cartilaginous roof, and the sides of the anterior portion of the nares. At a certain stage they form with the superior maxillary process a furrow running from the nasal furrow to the eye, the lachrymal fissure.

In the beginning the mouth is a large sinus, but is soon separated into a lower and larger digestive and an upper and smaller respiratory portion. This separation is brought about by the development, from the superior maxillary processes of the first branchial arch, of the palatal plates, which from the eighth week on blend into each other and at the same time unite with the lower border of the nasal septum. The union of the anterior portions of the palatal plates takes place earlier than that of the posterior portions.

Through union of the contiguous portions of the frontal and nasal processes with the superior maxillary processes the cheek is formed and a continuous superior maxillary border, from which are developed later the lip and the alveolar process of the upper jaw and intermaxillary bones, while the external portion of the nose develops from the frontal process. The intermaxillary bones are developed as independent bones, but unite very early with each other and with the upper jaw.

(d) *Faulty Closure of the Abdominal and Thoracic Cavities, and the Accompanying Malformations.*

§ 136. **Arrests of development of the ventral body-wall** may take place at different points and exhibit different grades of severity. They occur most frequently in the region of the umbilicus, where the closure of the abdominal cavity takes place latest. In the event of imperfect development of the abdominal wall at this point, so that this area is closed only by peritoneum and the sheath of the umbilical cord, and if these are pushed forward by the abdominal organs (Fig. 362), there is produced the condition known as **omphalocele**, or **umbilical hernia**. The umbilical cord is attached to the summit or at one side of the hernial sac, and is more or less shortened.

If the anterior abdominal walls wholly or in part fail to unite, there arise those conditions which are designated **fissura abdominalis,** or **gastroschisis completa** a n d **thoracogastroschisis.** These are characterized by the undeveloped abdominal coverings not having been separated from the amnion, but passing into it. The greater part of the abdominal organs lies in a sac formed by the amnion and

Fig. 362.—Hernia funiculi umbilicalis. Reduced to one-third.

peritoneum (*eventration*). The peritoneum, however, may be wanting, likewise the umbilical cord, and the umbilical vessels may pursue their course to the placenta independently.

A cleft confined to the thorax is called **thoracoschisis.** Should the heart, covered only with pericardium or free, protrude, the condition is designated **ectopia cordis.**

When the failure to close is confined to the region of the sternum, the condition is designated **fissura sterni.** This defect may involve the whole or a part of the sternum, at times affecting the bones, at other times only the skin.

The protrusion of the urinary bladder through a cleft in the abdominal wall is known as **ectopia vesicæ urinariæ.**

Clefts of the abdominal wall are not infrequently associated with clefts of the parts lying behind the wall, not only large clefts (total), but smaller ones (partial). When a cleft of the lower portion of the abdominal wall is associated with a cleft of the urinary bladder, so that the posterior wall of the latter protrudes through the abdominal fissure, the condition is known as **fissura,** or **exstrophia,** or **inversio vesicæ urinariæ.** Occasionally the pelvic girdle and the urethra are cleft, the latter being represented by a groove open anteriorly. The exstrophy is then said to be complicated by **fissura genitalis** and **epispadias.**

When an abdominal fissure or an abdominal and vesical fissure is combined with a fissure of the intestines, there is produced **fissura abdominalis intestinalis** or **vesicointestinalis.** The intestinal fissure is situated in the cæcum or beginning of the colon, and the mucous membrane of the cleft intestine protrudes through the opening in the same manner as the posterior wall of the bladder; the condition is called **exstrophia** or **inversio intestini.**

If the omphalomesenteric duct does not undergo normal involution, there remains at the lower end of the small intestine an appendix of intestine called **Meckel's diverticulum,** which arises perpendicularly from the outer margin of the intestine. It has the appearance of a glove-finger, and either swings free or is attached to the umbilical ring, sometimes being dilated at its end. In case of adhesion to the umbilical ring the intestinal mucosa may appear at the navel in the form of a tumor (*ectopia intestini, adenoma umbilicale*). In rare cases a cyst lined with mucous membrane may be formed in the abdominal wall (*omphalomesenteric cyst*).

Congenital fistulæ of the urachus, that is, fistulæ lying in the umbilicus and connecting with the bladder by a tract, depend on incomplete obliteration of the urachus or of the stalk of the allantois. They may be associated with an open or a closed urethra.

The development of the body-form from the flat embryonic primordium begins by snaring-off of the individual germ-layers from the outer embryonal area, and their folding to form two tubes, the body-wall and the alimentary canal.

The infolding of these layers takes place at the cephalic and caudal ends, as well as at the lateral portions of the embryonal primordium, and as the summits of the folds gradually grow together from all directions, those which form the body-wall produce a tube whose cavity finally communicates only at the parietal umbilicus, by means of a peduncle-like prolongation, with the cavity of the extra-embryonic portion of the blastoderm known at this time as the vitelline membrane. While the lateral and ventral walls of the embryo are being formed, in the body the intestinal furrow also closes to form a tube, which is in communication at only one point lying within the parietal umbilicus, known as the visceral umbilicus, with the cavity of the umbilical vesicle, by means of a channel known as the omphalo-mesenteric duct.

Umbilical hernia and clefts of the upper portion of the abdominal wall are frequently combined with craniorachischisis, while exstrophy of the bladder and intestine is often associated with myelocystocele. According to *von Recklinghausen,* the two malformations are to be regarded as coördinated with each other. Further, large abdominal clefts are often associated with lordotic and scoliotic curvatures of the spinal column.

(e) *Malformations of the External Genitalia and Anus, due to Arrested Development.*

§ 137. Malformations of the **external genitals** may be associated with malformations of the abdominal wall, bladder, and the internal genital organs, or may occur independently of these. **Complete absence of the external genitalia** occurs most frequently in connection with other mal-

formations of this region, particularly in the case of sirenomelia, (Fig. 363). The internal genitals usually are also malformed.

A **stunted condition** of **the penis** is not rare, the organ in consequence coming to resemble more or less the clitoris. This condition is usually associated with **hypospadias** — that is, the urethra opens on the under side, either beneath the glans, the body or the root of the penis, or even behind the scrotum (*hypospadias perineoscrotalis*). These malformations may exist in penises otherwise normally developed, and depend on partial failure of the sexual furrow to close.

Epispadias is that condition in which the urethral opening is found on the dorsum of the penis. It is more rare than hypospadias, and is dependent on defective or delayed closure of the pelvis, so that the cloaca, before the closure, becomes divided into an intestinal (anal) and a genital opening. Under certain conditions the penis remains cleft throughout its length; at the same time a fissure of the bladder and abdomen may be present.

Hypertrophy of the prepuce is not rare. If the preputial opening is narrowed so that the prepuce cannot be drawn back over the glans, the condition is designated **hypertrophic phimosis**. **Total absence of the prepuce** is rare; **abnormal shortness** is more frequent.

Defective development of the scrotum is usually associated with retention of the testicles in the abdominal cavity or in the inguinal canal, and leads to appearances whereby the external genital organs of the male resemble those of the female, especially when the penis is stunted.

Fig. 363.—Complete absence of the urethra and external genitals, with extreme distention of the body due to an enormous dilatation of the bladder. Compression and stunting of the lower extremities. (In the posterior wall of the bladder rudiments of a female genital apparatus in the form of portions of the tubes and ovaries were found.)

In the female the **clitoris** as well as the **labia majora** and **minora** may show **stunted development**. **Epispadias** and **hypospadias** also occur in the female sex, the former coincidently with a fissure of the abdominal and bladder walls. In hypospadias a portion of the posterior wall of the urethra is lacking, and the urethral opening may be found within the vagina.

Absence of the urethra occurs in both sexes (Fig. 363). In girls the bladder may open directly into the vagina.

Closure (atresia) of the urethra likewise occurs in both sexes, and results either from a partial defect of the same or from obliteration of the orifice. Accumulation of urine in the bladder may lead to marked dilatation of the viscus (Fig. 363).

Abnormal narrowness of the urethra may exist in a portion of its course or throughout its length. Further, its lumen may be narrowed as the result of hypertrophic development of the colliculus seminalis.

In rare cases multiple orifices of the urethra have been observed. Further, in men there may be found in the glans penis a blind tube lying beside the urethra.

Atresia ani simplex is closure of the anus, the intestine being at the same time well developed. It may arise from failure of the ectoderm to fold in at the anal site, or a cloaca already existing and opening outward may again become closed through adhesions. If the rectum does not end immediately above the anal membrane but higher up, there exists in addition to the atresia ani **atresia recti,** a malformation which may occur even when the anus is well developed.

When, with absence of the anus, there is also arrested development of the vaginal wall, which grows downward, between the sinus urogenitalis
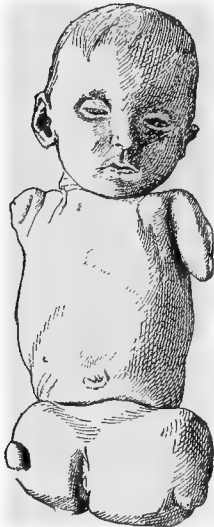
FIG. 364.—Amelus.

FIG. 365.—Micromelus with cretin-like facies.

and intestine, to unite with the perineum, there remains a cloaca in which the sinus urogenitalis and the end of the bowel unite. In other cases there are found **fistulous communications between the rectum** and the **bladder** or **urethra** (in boys), or between the **rectum** and the **vagina** or **uterus** (*atresia ani vesicalis, urethralis, vaginalis, uterina*).

In rare cases the intestine, in anal atresia, may open by **external fistulæ** in the perineum, scrotum, or sacrum. External fistulæ below the anus may occur as remains of the post-anal gut.

(f) Malformations of the Extremities due to Arrested Development.

§ 138. **Defective development of the extremities** is not rare, and is to be referred to primary defect of the primordium of an extremity, to disturbance in the later development of the limbs or the bones, and to constrictions caused by strands of fœtal membranes or by loops of the umbilical cord. Defective development of the extremities may also follow malformations of the central nervous system. The following forms may be distinguished:

(1) *Amelus.* The extremities are completely absent; in their place are found warty or stump-like rudiments. The trunk is usually well formed (Fig. 364).

(2) *Peromelus.* Stunting of all the extremities.

(3) *Phocomelus.* The hands and feet are alone developed and are attached directly to the shoulder and pelvis respectively.

(4) *Micromelus.* The extremities are developed, but are abnormally small (Fig. 365).

(5) *Abrachius* and *Apus.* Absence of upper extremities with well-developed lower ones, or *vice versa.*
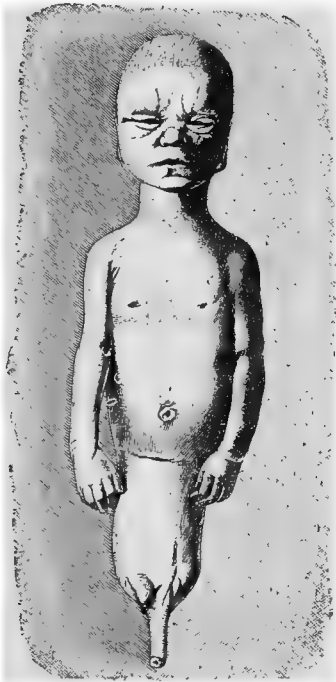
FIG. 366.—Sympus apus.
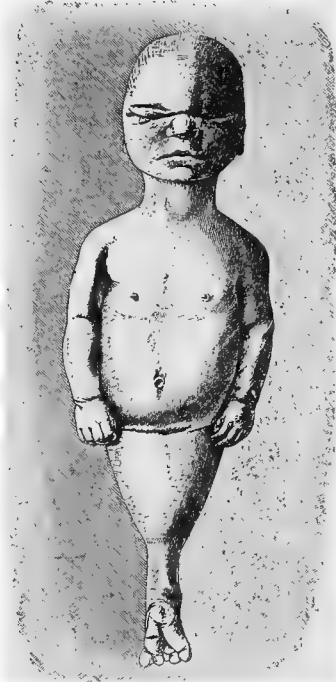
FIG. 367.—Sympus dipus.

(6) *Perobrachius* and *Peropus.* Stunting of the upper or lower extremities.

(7) *Monobrachius* or *Monopus.* Absence of one of the upper or lower extremities.

(8) *Sympus, Sirenomelia, Symmelia.* The lower extremities are fused (Figs. 366, 367), and rotated on their axes so that their external aspects are in contact. The pelvis is usually defective, as are also the external genitalia, the bladder, urethra, and anus. At the end of the blended extremities feet may be entirely wanting (*sympus apus*) and only a few toes may be present; in other cases one (*sympus monopus*) or both feet may be present (*sympus dipus*).

(9) *Absence of individual bones* may occur in any part of the extremities.

(10) *Perodactylism* — *stunting of the fingers of toes* — appears in a great variety of forms, but in general is seen as defective development (*brachyphalangism*) or absence of individual phalanges, or as membranous or bony connections between the fingers (*syndactylism*).

If only the outer fingers or toes are developed while the middle ones are lacking, there arise those formations designated *cleft-hand* and *cleft-foot*. In more extensive malformations of the fingers there occur defects in the region of the tarsal and metatarsal bones or carpal and metacarpal bones respectively. These malformations are designated respectively *peropus* and *perochirus*. Absence of the hand or foot is known as *achirus* or *apus*.

§ 139. Among the abnormal positions of the extremities **congenital luxations** (slipping of the articular heads from their sockets) are of special interest. They are most common at the hip-joint, rare at the elbow-, shoulder- and knee-joints. Congenital luxations are due to *local arrests of development,* but may be the result of mechanical influences. In the hip-joint the disturbance of development results in a small and imperfect acetabular socket, and the head of the femur is more or less imperfectly developed. The small acetabulum lies in the normal position, but the head of the femur is displaced, most often backward (luxatio iliaca). At birth the ligamentum teres is intact, and the capsule of the joint covers both the head of the femur and the acetabulum. After much use of the leg the ligamentum teres becomes stretched and may tear, the capsule becomes dilated and bag-like, and, at the point where it is pressed against the bone, may become perforated. A new joint may then be formed through proliferation of the surrounding tissues.

Abnormal positions of the feet and hands are to be referred partly to disturbances of development and partly to mechanical influences exerted on the extremities during their growth. The most important is **congenital club-foot (pes equinovarus).** The foot is left in the fœtal position, with accompanying abnormal development of the bones and their articular surfaces. The inner border of the foot is sharply elevated, and the foot at the same time is brought into plantar flexion. The colium tali is elongated in an anterior and inferior direction. If children thus afflicted learn to walk, they tread on the outer side of the foot, which becomes flattened, while the foot becomes still more sharply turned inward.

Congenital club-foot, though usually to be regarded as a primary disturbance of development, may also be caused by *pressure* due to a relatively small uterus. Under these conditions those pathological positions of the foot known as **pes calcaneus** and **pes valgus** also develop, and are characterized by strong dorsal flexion and by outward twisting of the foot. Frequently the evidences of pressure to which the feet have been subjected are seen in atrophy of the skin and portions of the bones.

The position of the hand known as **club-hand** or **talipomanus** is caused by rudimentary development of the radius, and is usually associated with other malformations.

2. ABNORMAL POSITION OF THE INTERNAL ORGANS AND OF THE EXTREMITIES.

§ 140. Of the abnormal positions of the internal organs, the most important is known as **situs inversus viscerum** — i.e., *lateral transposition of the internal organs,* so that the thoracic and abdominal organs form a mirror-image of the normal position. This condition has been observed

both in double monsters and in single individuals. It is entirely compatible with life, and may be restricted to the heart alone, or to the abdominal organs, or to a part of the latter (*situs irregularis*). Abnormal positions occur especially often in the abdominal organs. For example, the kidney is not infrequently found in an abnormal position (*dystopia renis*), usually low, so that it approaches the sacral promontory or lies in front of it. The testis is not rarely retained in the abdominal cavity (*ectopia interna,* or *abdominalis testis,* or *cryptorchismus*), or in the inguinal canal (*ectopia inguinalis*), or at the external ring (*ectopia pubica*), or in the fold between the thigh and scrotum (*ectopia cruroscrotalis*), or in the perineal region (*ectopia perinealis*), or in the fold of the groin (*ectopia cruralis*). *Abnormal positions of the intestines,* particularly of the colon, are not rare.

3. Malformations due to Excessive Growth or Multiplications of Organs or Body-parts.

§ 141. The malformation known as giantism occurs as the result of excessive growth of the entire body, during intra-uterine life or later. During extra-uterine life such growth may occur that the size of the individual far exceeds the maximum normal limits.

Fig. 368—Polydactylism with forking of the hand. (After Lancereaux.)

Partial giant growth may take place during intra-uterine life or after birth. The head and portions of the extremities are usually affected. *Unilateral giant growth* is restricted to half of the face or to one extremity, although in rare cases the hypertrophy may involve all the parts of one side: face, trunk, and extremities.

Should other tissues become increased, as in the extremities, trunk, or face, so that malformations resembling the skin of the pachyderms are produced, the growth is designated **elephantiasis** (see § 76, Figs. 109, 110).

Circumscribed hypertrophies of bones occur in various portions of the skeleton, and are sometimes multiple. The bones of the skull as well as those of the face may be affected. There are cases in which hypertrophy may be so extensive that one or both of these regions show marked disfiguration, the condition being known as *leontiasis ossium* (Fig. 115. On the trunk and extremities local growths of bone may lead to enlargement of single bones or to atypical excrescences known as exostoses.

§ 142. The **occurrence of supernumerary organs, or of multiplication of parts of the skeleton,** and of **the muscular system,** is relatively frequent.

1. **Duplication of the extremities.** Duplication of an entire extremity without duplication of the pelvic or shoulder bones has not been observed in man. Duplication of the hands and feet is rare (Fig. 368). The number of fingers may reach nine or ten. Much more frequent is **multiplication of the fingers or toes (polydactylism)** on a single hand (or foot respectively), in which condition the super-

numerary fingers (or toes) are attached at the ulnar or radial side (or tibial and fibular sides, respectively), or intercalated between the others. Often the fingers are duplicated only in part — that is, by cleavage of the first or the first and second terminal joints. Those attached at the margin of the hand may be well developed or rudimentary. Occasionally they appear as pedunculated fibrous growths. In the fully developed supernumerary fingers or toes the phalanges may articulate with the metacarpal or metatarsal bones of a neighboring finger or toe, or with their own (supernumerary) carpal or tarsal bones. Polydactylism in certain cases is inherited and is therefore dependent on intrinsic causes.

2. **Supernumerary nipples and breasts (hyperthelia, hypermastia)** are not uncommon in both sexes, and are probably to be regarded as a reversion to polymastic racial ancestors. The supernumerary organs are usually situated on the thorax, along two lines converging from the axillary to the inguinal regions, but in rare cases may be found elsewhere — in the axilla, on the shoulder, on the abdomen, back or thigh. They are usually small, but in the event of pregnancy may take on functional activity. The number of nipples may reach as high as ten.

3. The **formation in men of breasts** resembling those of women (*gynæcomastia*) is rarely seen in well-developed men with normal sexual apparatus (see Hermaphrodism, § 143), but it not infrequently happens that the male breast undergoes moderate enlargement at the time of puberty.

4. **Duplication of the penis** is of rare occurrence, and may be associated with the formation of two urethræ having independent openings into the bladder, and with two scrota, the two penises being typically developed.

5. **Supernumerary bones** and **muscles** are of frequent occurrence. *Supernumerary vertebræ* may be found in any part of the spinal column; and at its lower end may cause lengthening, resulting in the formation of a **tail**. Three forms of tails may be distinguished: true tails containing bones; false or imperfect tails which represent an elongation of the vertebral column, but contain neither cartilage nor bones (so-called pig's tail); and tail-like appendages of skin which consist of different forms of tissue, and are to be classed with the teratomata. True tails are rare; they are more often the result of separation or elongation of the vertebræ than of an increase in their number.

Reduplication of the phalanges of one finger is rare.

Supernumerary ribs in the neck or lumbar region, as well as forking of the ribs, are not rare.

Supernumerary teeth occur.

6. **Duplication** or **cleavage of the primordium** of the **thoracic** and **abdominal organs** occurs most frequently in the case of the spleen, pancreas, adrenals, ureters, pelvis of the kidneys, and lungs, more rarely in that of the ovary, liver, kidney, testicle, and bladder.

4. True and False Hermaphrodism.

§ 143. The fact that the sexual organs of both sexes develop from originally similar primordia makes it *a priori* probable that malformations might result through unequal development of the right and left sides,

or through simultaneous development of organs peculiar to both sexes, or through lack of harmonious development of the external and internal genitals.

Those malformations which are characterized by the fact that. the sexual apparatus of a single individual contains parts belonging to both the male and female, are grouped under the designation **hermaphrodismus.** When both sexual glands (testis and ovary) are present the condition is called **hermaphrodismus verus** (*hermaphrodismus glandularis*). If the mixing of sexual characteristics consists of a combination of male and female genital passages with the external genitalia of the opposite sex, the condition is known as **pseudohermaphrodismus.** The true sex is determined by the nature of the sexual glands.

The build of hermaphrodites frequently shows a curious mixture of male and female characteristics. For example, the breasts, neck, and shoulders may correspond to the female type, while the beard, face, larynx, and voice correspond to the male type. In false hermaphrodites the body characteristics do not always correspond to the true nature of the sexual glands; a male may resemble a female and *vice versa*.

The following **types of hermaphrodism** may be distinguished:

I. **Hermaphrodismus verus** or **androgynes.**—1. *Hermaphrodismus verus bilateralis,* or double-sided hermaphrodism, is characterized by the presence on both sides of both ovary and testis, or the presence on both sides of an organ containing both ovarian and testicular tissue. *Heppner* asserts that in a nine-months-old child, having hermaphroditic external genitals, with vagina, uterus, and tubes, both ovary and testis were found in the broad ligament; epididymis and vas deferens were wanting.

2. *Hermaphrodismus verus unilateralis,* or one-sided hermaphrodism, is that condition in which on one side there exists but one sexual gland, while on the other both testis and ovary are present. *Salén* has reported a case of a woman of forty-three years of age, who had menstruated since her seventeenth year, in whom there was found on the right side (castration on account of uterine myoma) a hermaphroditic gland, the nature of which was confirmed by microscopic examination. The ovarian portion of the gland was typically developed; the epithelium of the seminiferous tubules of the testicular portion consisted of follicular cells and cells of Sertoli, but lacked spermatogonia and seminal cells. *Blacker* and *Lawrence* have also described a case of hermaphroditic gland occurring in a child still-born at eight and a half months. In the hernial sac of an individual twenty years old *Garré* demonstrated the presence of a tube and both sexual glands with parovarium and epididymis (the microscopic examination was made by *Simon*).

3. *Hermaphrodismus verus lateralis* is that condition in which there is an ovary on one side and a testis on the other. It has been many times observed in man, though in the majority of cases no careful microscopic examination was made, and when carried out, ovarian tissue could not with certainty be demonstrated. *Obolonsky* reported a case (a twelve-year-old girl) in which histological examination showed on the right side a testicle, and on the left side an ovary, but it is to be noted that ova were not seen in the latter. The right broad ligament contained a testis, an epididymis, a vas deferens, a rudimentary tube, a round ligament; the left broad ligament contained an ovary, with an ovarian ligament, and a well-developed tube. Moveover, a uterus, vagina, and also a prostate were present. According to reported observations, the corresponding sexual passages may be present or in part wanting. The external genitals are malformed, and combine structures belonging to both sexes.

II. **Hermaphrodismus spurius, or pseudohermaphrodismus,** is characterized by bisexual development of the sexual passages and external sexual organs in association with the unisexual development of the essential sexual gland. The most pronounced cases occur in males, who, in addition to their proper sexual organs, possess a more or less well-developed vagina, uterus, and tubes. It is much more rare to find in females development of a portion of the Wolffian duct.

In male false hermaphrodites the external genitals are frequently malformed and approach the female type, while in female false hermaphrodites the external genitals resemble those of the male.

The resemblance of the male external genitals to those of the female is brought about by stunting of the penis and total or partial failure of the sexual furrow in the penis to close (hypospadias), so that the two halves of the scrotum are separated, leaving a depression beneath the root of the penis, which represents the remains of the sinus urogenitalis. The scrotal halves come, therefore, to resemble the labia majora, particularly in non-descent of the testicles. The external genitals of the female approach in appearance those of the male through development of the clitoris into a sort of penis, while the vaginal opening is narrowed or closed through union of the labia. The vagina and urethra have a common opening, or open separately beneath the penis-like clitoris.

The atypical development of the external genitals may or may not be associated with malformations of the sexual passages, and is, therefore, not dependent on malformations in other portions of the sexual apparatus.

1. *Pseudohermaphrodismus masculinus* occurs in three varieties:

First, *pseudohermaphrodismus masculinus internus,* in which the external genitals are of the male type, and the prostate is developed, but is usually pierced at the colliculus seminalis by a canal opening into the urethra, the former being continued above into a rudimentary or more or less well-developed vagina, often into a more or less well-formed uterus, and even tubes. The male organs may be well developed or malformed.

Second, *pseudohermaphrodismus masculinus completus,* or *externus et internus,* in which the vagina, uterus, and tubes are present in rudimentary or more or less complete development, while the external genitals resemble the female type. The penis presents the condition of hypospadias and resembles the clitoris; beneath it lies a furrow at whose posterior end there is usually an orifice leading into a short vestibule which divides at once into a urethra and a vagina. Sometimes the vagina and vestibule are separate. In rare cases the external genitals appear normal, but the penis contains a double canal, the upper one representing the urethra, the other the sexual passage. In the case of more marked development of the ducts of Müller the vasa deferentia are frequently defective, and the seminal vesicles are sometimes wanting.

Third, *pseudohermaphrodismus masculinus externus,* in which only the external genitals depart from the male type, and resemble the female. Since in these cases the bodily habitus often simulates that of the female, the sex of the individual may easily be mistaken.

2. *Pseudohermaphrodismus femininus* also occurs in three similar varieties, but is much more rare.

In *pseudohermaphrodismus femininus internus* rudiments of the Wolffian ducts, lying in the broad ligament or in the uterovaginal wall, and sometimes extending to the clitoris, are found in association with well-developed external genitals.

Pseudohermaphrodismus femininus externus is characterized by external genitalia resembling those of the male.

Pseudohermaphrodismus femininus externus et internus, in which the external genitals resemble those of the male and there is persistence of parts of the Wolffian ducts, is rare. Of the internal male genitalia, there was found in one case a prostate, and in another case a prostate pierced by the vagina, an ejaculatory duct, and a sac resembling a seminal vesicle, which opened into the vagina.

The **internal sexual organs** develop from the same undifferentiated primordium in both males and females. These consist of a sexual gland lying on the medial anterior side of the *Wolffian body,* and a *sexual passage* known as the *duct of Müller.* The latter develops beside the *Wolffian duct,* and, like it, empties into the lower end of the bladder or into the sinus urogenitalis.

In the *male* the *duct of Müller* disappears, only traces in the form of the uterus masculinus or vesicula prostatica remaining; the primitive sexual gland unites with a small part of the *Wolffian body,* which becomes the head of the epididymis, another small portion forming the vasa aberrantia testis (organ of *Giraldes*), the remainder disappears, while the *Wolffian* duct becomes the vas deferens and vesicula seminalis.

In the *female* the *Wolffian body* and its *duct* disappear, leaving only a trace in the form of gland-tubules known as the parovarium, but remains of the duct are not infrequently found in the uterine wall. From the *ducts of Müller,* which in part coalesce at their lower ends, develop the vagina, uterus, and tubes. The extreme upper end of the duct of *Müller* not infrequently persists in the form of

a little pedicled sac attached to the abdominal end of the tube, the hydatid of *Morgagni*.

The primordia of the *sexual glands* appear in the fifth week. In mammalia (probably also in man) they develop through localized thickening of the peritoneal epithelium, which becomes the germinal epithelium, while at the same time the mesoderm proliferates. Whether the seminal tubules arise from peritoneal epithelium (*Bornhaupt Egli*), or whether they are derived from an ingrowth of the Wolffian body into the testis (*Waldeyer*), is an undecided question (*Kölliker*). The ova arise from germinal epithelium. The environing cells of the Graafian follicle are regarded by *Waldeyer* as derived from the germinal epithelium; while *Kölliker* believes that they arise from the Wolffian body.

The significance of the *pedunculated* and *non-pedunculated hydatids*, found in varying numbers near the globus major of the epididymis, is not yet determined (*Kölliker*). The non-pedunculated cyst known as the hydatid of Morgagni is regarded by *Waldeyer* as a remnant of the duct of *Müller*. According to *Roth*, it may stand in close relation to the *Wolffian* body, inasmuch as there is occasionally found a vas aberrans of the epididymis communicating with it.

In the development of the vagina and uterus the ducts of *Müller* and the *Wolffian* ducts unite at their lower portion to form the genital cord. At the end of the second month the ducts of *Müller* blend to form a single canal, which then develops into the vagina and uterus. This union takes place near the middle of the genital cord. The Wolffian ducts play no rôle, though remains of these are found at birth in the broad ligament and in the wall of the uterus. According to observations of *Riedel,* remains of the Wolffin duct are found in about a third of adult females, in the form of a tube lined by cylindrical epithelium surrounded by muscle, or as a muscle-bundle without epithelium, lying anteriorly and to the side of the uterus and vagina.

The **external genitals** begin to develop, even before the cloaca has separated into the intestinal and genito-urinary orifices, by the formation, in the sixth week, of a median genital tubercle in front of the cloaca, and further, of two lateral folds, the genital folds. Toward the end of the second month the tubercle becomes more prominent, and shows on its lower surface a furrow, the genital furrow. In the third month the cloaca becomes divided to form the anal and genito-urinary openings. In the male embryo the genital tubercle becomes the penis, the glans being recognizable as early as the third month. In the fourth month the furrow closes to form a tube; at the same time the two genital folds unite to form the scrotum.

The prepuce is formed in the fourth month. The prostate arises in the third month as a thickening of the tissues at the junction of the urethra and the genital cord. The glands of the prostate develop in the fourth month from the epithelium of the canal and grow into the surrounding connective tissue.

In the female embryo the closure of the genital furrow and the genital folds does not take place, so that the sinus urogenitalis remains short. The genital eminence becomes the clitoris, the folds become the labia majora, and the edges of the genital furrow the labia minora.

5. Double Monsters.

(a) Classification of Double Monsters.

§ 144. Twin-formations lying in a single chorion may be divided into two large groups: *twins completely separated from one another,* and *twins united by some portion of their bodies.*

Of the **twins completely separated from one another** there may be distinguished two types; one in which *both twins are fully developed,* and one in which *one twin is stunted.*

Twins joined by portions of their bodies may likewise be divided into two groups: *twins showing uniform development* and *twins showing unequal development.* To the latter belongs a group of stunted parasitic forms that may be classed as teratomata.

According to the situation of the duplicated portions of the body, there may be distinguished:

1. Monstra duplicia katadidyma or duplicitas anterior.
2. Monstra duplicia anadidyma or duplicitas posterior. '
3. Monstra duplicia anakatadidyma or duplicitas parallela.

These may be divided into three classes:

1. Twins united chiefly by the epigastrium and thorax.
2. Twins united chiefly by the heads.
3. Twins united chiefly by the pelves.

Ahlfeld divides the double monsters into two groups, those with *complete* and *those with partial doubling of the axial structures.*

In rare instances **triple monsters** occur.

(b) The Chief Forms of Double Monsters.

§ 145. **Twins separated from each other** and lying in a *single chorion* are designated **homologous twins.** They are always of the same sex, have usually a common placenta, and resemble each other closely. If one of the twins should die after its body has been developed, it may be pressed flat by the growth of its fellow, giving rise to the condition known at **fœtus papyraceus.**
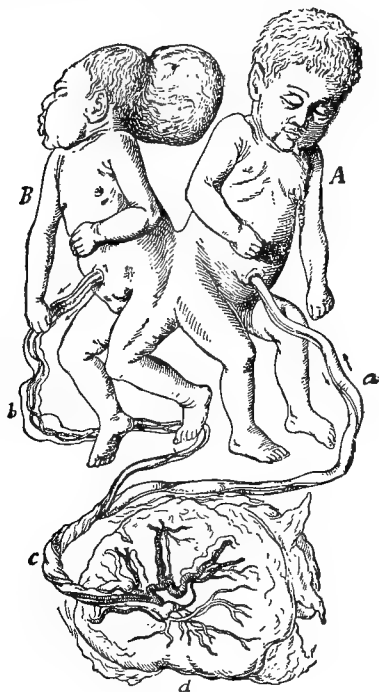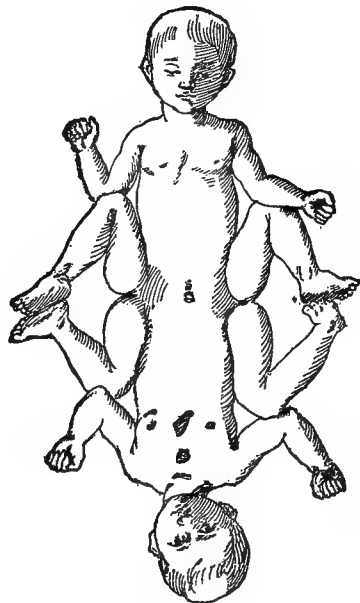
FIG. 369.   FIG. 370.

FIG. 369.—Pygopagus. (After Marchand.) *A, B,* The two twins; *a, b,* separated umbilical cords; *c,* blended umbilical cords; *d,* common placenta. There is a single coccyx and sacrum (from the second vertebra downward), and the lower end of the medullary canal is single. The two intestinal canals terminate in one anal opening. Vestibule of vagina single, the remaining portions of the sexual organs double.

FIG. 370.—Ischiopagus. (After Levy.)

When twins possess a common placenta in which the blood vessels have abundant anastomoses, the heart of the stronger fœtus may control the circulation and thereby cause changes in the direction of the blood-stream in the weaker twin. As a result of this the latter suffers disturbances of development, and becomes changed into an **acardius,** a *monster without a heart,* developing no heart at all or a rudimentary one. In the majority of such cases the *head also fails to develop (acardius acephalus)* or remains *rudimentary (acardius paracephalus),* and likewise there is usually no development, or only a rudimentary one, of the upper extremities, thorax walls, lungs, and liver, while the abdomen, pelvis, and lower
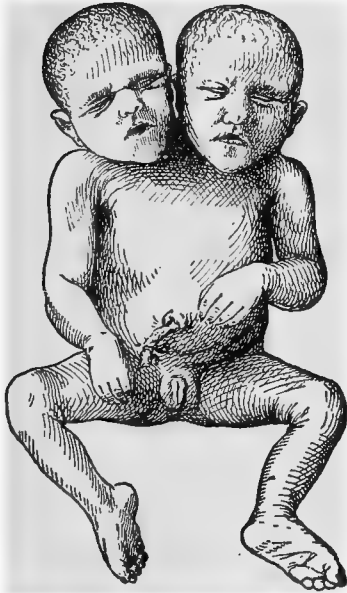
Fig. 371.—Dicephalus dibrachius dipus.

Fig. 372.—Diprosopus distomus tetrophthalmus diotus dibrachius.

extremities are more or less perfectly formed. According to the development of the extremities the following varieties may be distinguished: *acardius paracephalus (or acephalus) sympus, monopus, dipus, monobrachius, dibrachius.*

In rarer cases there is no recognizable development of any part of the body, and there is formed an *acardius amorphus,* consisting of a shapeless mass covered with skin, usually without any indication of extremities and possessing only rudiments of organs.

Of rare occurrence is the formation known as *acardius pseudoacormus* — that is, a monster in which the head only is developed, while the other parts of the body are represented by rudiments.

§ 146. **Twins equally developed and united** occur in the following types:

27

1. **Duplicitas anterior** (*monstra duplicia katadidyma*). Anterior duplication with union of posterior portions of the body.

Pygopagus (Fig. 369). Union of twins in the region of the coccyx or of the sacrum. According as the union is more or less extensive, the sacrum, coccyx, lower end of the medullary canal, anus, lower end of the bowel, and the sexual apparatus are doubled or single.

Ischiopagus (Fig. 370). Union of twins in the pelvis, which forms a wide ring, the two sacra being placed opposite each other. The anus, lower end of the bowel, and the sexual organs may be single or double, and the number of the lower extremities two to four.

Dicephalus (Fig. 371) and **diprosopus** (Fig. 372). The duplication is limited to the upper part of the trunk and head, or to the neck and head, or the head alone, or, finally, to portions of the head. As the external blend-

FIG. 373.

FIG. 373.—Craniopagus parietalis.

FIG. 374.—Cephalothoracopagus or syncephalus, with janus head. Both anterior and posterior faces are malformed, and possess but one eye, while the nose is represented by a proboscis-like organ situated above the eye.

FIG. 374.

ing increases in extent, there occurs blending of the internal organs, the intestine, liver, lungs, heart, spinal cord, brain, etc. According to the number of the lower and upper extremities there may be distin-

guished *dicephalus tetrapus, dipus, tetrabrachius, tribrachius, dibrachius* (Fig. 371). When the heads have blended there may be distinguished *diprosopus tetrophthalmus, triophthalmus, diophthalmus, tetrotus, triotus, diotus, distomus, monostomus, tribrachius and dibrachius* (Fig. 372).

The mildest grades of duplicitas anterior are represented by *duplication of the jaw, mouth, or nose.*

2. **Duplicitas posterior** (*monstra duplicia anadidyma*). Union of the twins at the head and thence downward with duplication of the posterior parts of the body.

Craniopagus (Fig. 373). Union of twins in the cranial region. According to the site of union there may be distinguished *craniopagus pari-*

Fig. 375.—Thoracopagus tribrachius tripus. The hand of the third arm, common to both halves, possesses two dorsal surfaces, and the laterally distorted fingers possess nails on both sides. The common third foot has eight toes.

etalis, frontalis, occipitalis. When the union is more extensive portions of the brain are single.

Cephalothoracopagus or **syncephalus** (Fig. 374). Blending of twins in the region of the forehead and face, and of the abdomen. In the region of the united heads there is an anterior and a posterior face (*janus, janiceps*). The two faces may be equally (*janus symmetros*) or unequally developed (*janus asymmetros*), one face being well developed, the other imperfectly. The internal organs present different degrees of blending into single organs.

Dipygus. The duplication is limited to the lower half of the body and the lower extremities, while the upper parts are single or partly cleft. The duplication of the spinal cord may begin at different heights. According to the number of extremities different forms may be distinguished.

The mildest grades of duplication are confined to the lower end of the spinal column, the anus, and the external genitals.

3. **Duplicitas parallela** (*monstra duplicia anakatadidyma*). Duplication of the anterior and posterior ends of the body with parallel positions of the trunk.

Thoracopagus (Fig. 375). Union of twins by the thorax. According to the site and extent of the union, as well as the number of extremities present, there may be distinguished different forms, particularly the following: *xiphopagus* (union at the xiphoid process), *sternopagus*
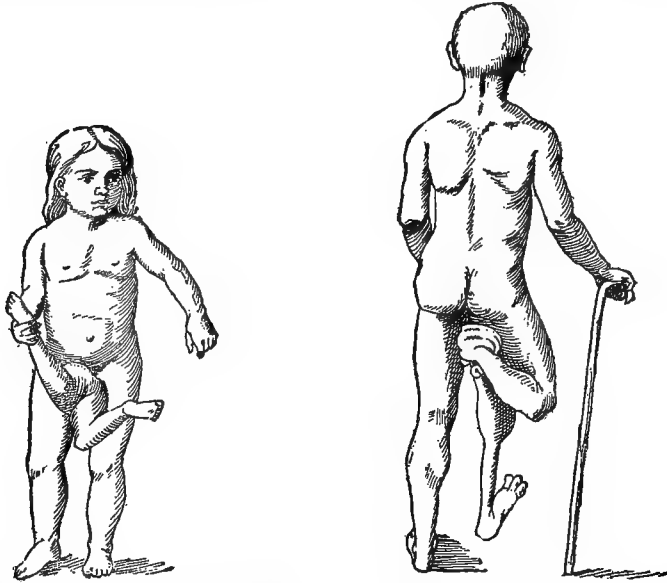
FIG. 376.—Polymelos. (After Lancereaux.)   FIG. 377.—Polymelos. (After Liesching.)

(union at the sternum), *thoracopagus tetrabrachius, tribrachius, dibrachius, tetrapus, tripus,* and *dipus.* When portions of the faces have blended there results *prosopothoracopagus.* Blending of the internal organs into single organs varies with the degree of external blending. The heart may be double or single, in the latter case malformed. Thoracopagus is relatively frequent.

Rachipagus. Blending of twins in the region of the spinal column is rare.

§ 147. **Twins joined but unequally developed** may occur in any of the double forms described in § 146. If the development of one of the twins remains rudimentary and if its heart does not develop, its nourishment can come only through its well-developed fellow. The better developed of the two is then known as the **autosite,** the other as the **parasite.** If the parasite is of markedly rudimentary development, it may be classed with the **bigerminal teratomata** (cf. §§ 127 and 128).

At the *posterior ends of the body* there may occur a rudimentary double monstrosity in the form of *increase in the number of the extremities, polymelos* (Figs. 376, 377). In so far as the lower extremities are concerned such a malformation may be classed as an ischiopagus or a

dipygus. The supernumerary extremities may be one or two in number, and more or less well developed. Further, there not infrequently occur *coccygeal teratomata* in which the presence of rudimentary extremities
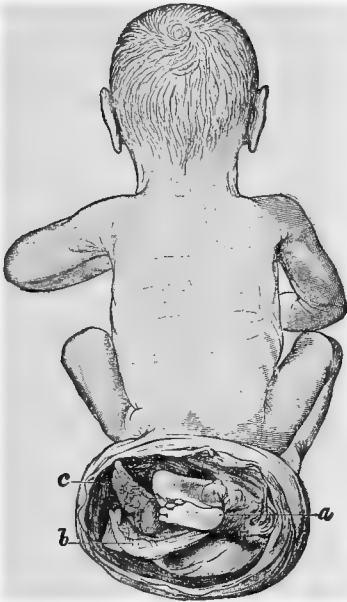
FIG. 378.

FIG. 379.

FIG. 378.—Bigerminal teratoma of the coccygeal region (pygopagus parasiticus.) *a, b, c,* Extremities lying in a sac formed by the skin of the autosite.

FIG. 379.—Thoracopagus parasiticus (thoracomelus). Three legs spring from the pelvis; one of them has a double foot. Two upper extremities project from the anterior chest-wall.

FIG. 380.

FIG. 381.

FIG. 380.—Thoracopagus parasiticus. (After Schenk von Gräfenberg.) Parasite attached to chest of autosite.
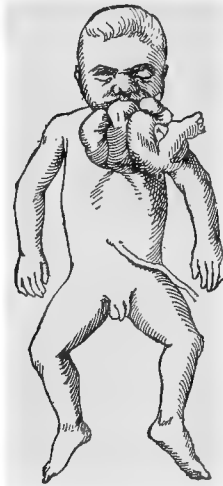
FIG. 381.—Epignathus. (After Lancereaux.)

(Fig. 378, *a, b, c*) or of various body elements leaves no doubt that the tumor-like formation covered by the skin of the autosite is to be regarded as a double monster, a *rudimentary pygopagus,* or as *dipygus parasiticus.* Such a parasite is designated *epipygus.*

Supernumerary extremities (Fig. 379) may also be found on the trunk or *there may occur a headless trunk with extremities* (Fig. 380), or a *rudimentary thorax without extremities,* or, finally, *teratomata* which may be interpreted as *thoracopagus parasiticus (omphalopagus)* and as *dipygus parasiticus.* The malformation is also called *epigastrius.*

The inclusion of such teratomata beneath the skin of the abdomen or thorax, or in the abdominal or thoracic cavities of the autosite, gives rise to the condition known as *inclusio fœtalis subcutanea,* or *abdominalis,* or *mediastinalis.*

In the *region of the head* rudimentary twin-formations appear most often in the mouth cavity, forming an amorphous mass, firmly attached to the base of the skull, consisting of skin, connective tissue, cartilage, bone, brain-tissue, teeth, intestinal elements and muscle, and, rarely, developed extremities. Such malformations are included under the designation *epignathus* (Fig. 381).

On other parts of the head (*prosopopagus parasiticus*) rudimentary twin formations or bigerminal teratomata are rare (cf. §§ 127, 128); they also occur in the cranial cavity (*encranius*) and in the neck (*hygroma colli*).

CHAPTER X.

The Pathogenic Fission-Fungi and the Diseases Caused by Them.

I. General Considerations Regarding the Schizomycetes or Fission-fungi.

1. General Morphology and Biology of the Fission-fungi.

§ 148. The **Schizomycetes** or **fission-fungi,** designated collectively as **bacteria,** belong to the *protophytes* — that is, to the smallest and simplest forms of plant-life. Many of them are so small that they stand on the border-line of invisibility even with the use of the highest-power objectives and eye-pieces. In animal tissues, it is frequently difficult to distinguish them from the products of cell-disintegration; often this can be accomplished only through the employment of specific reagents or staining-methods, and occasionally only through culture experiments.

The *Schizomycetes* are *non-chlorophyllaceous, unicellular organisms,* but as a result of growth and multiplication they form colonies of cells.

The form and character of single cells, as well as their manner of growth, division, and multiplication, vary greatly, and these differences are used as a basis for the classification of bacteria. In the first class are placed the **Cocci,** often designated *Micrococci,* or that form of bacteria which occurs in the form of *spherical* or *oval cells.* There may be distinguished six forms of cocci: *double-cocci* or *Diplococci, chain-cocci* or *Streptococci, clustered cocci* or *Staphylococci, tablet-cocci* or *Merismopedia, packet-shaped cocci* or *Sarcinæ,* and *tube-cocci* or *Ascococci.*

The second class constitutes the **Bacilli** (rod-shaped bacteria). Long thread-like bacteria are called *Leptothrix.*

To the third class belong the **Spirilla** (screw-shaped bacteria). Screw-shaped forms with short, wide turns are known as *Spirilla,* those with drawn-out turns as *Vibrios,* those with a long, closely wound screw as *Spirochætes.*

The Schizomycetes are composed of **cell-contents** and **cell-membrane,** both of which consist of an albuminoid body, which varies with the species. Many bacilli contain fat in their cell-bodies, at times so abundantly that it may be demonstrated by staining with Sudan III. Some of these bacteria (tubercle-bacillus, lepra-bacillus, and actinomyces) show the presence of fat both when growing in living tissues and when cultivated on artificial media; others (staphylococcus aureus, anthrax-bacillus, bacillus of glanders) show the presence of fat only when grown on special media. In many forms of bacteria the membrane may appear as a hyaline *capsule* surrounding the cell.

In all forms of bacteria, with the exception of the cocci, there have been observed swarming **movements** which are brought about by fine thread-like **flagella** attached at the ends or scattered over the entire cell. In addition there occur slow oscillatory or gliding and creeping

movements which are dependent on the contractile and flexible qualities of the plasma. Both forms of motion occur only under certain conditions of nutrition and growth, and only in certain species.

Multiplication of bacteria takes place through **transverse division** of cells which have previously become elongated. In some forms division can take place in two or even three dimensions. After division the cells separate immediately or remain for a time attached to each other. When the cells remain attached after dividing transversely, **threads** are formed (*Streptococcus, Leptothrix*); after dividing both transversely and longitudinally, **flat, tablet-like colonies;** after dividing in all three dimensions, **colonies resembling a solid body** (*Sarcina*) are produced. Long threads may become segmented into shorter pieces.

If resting bacterial cells, as the result of constantly progressing reproduction or through the accumulation of neighboring cells, heap themselves in masses, there are formed colonies, which are called **zoöglœa.**

Many of the bacteria form *spores.* These cells are distinguished by the fact that they remain alive under conditions in which ordinary forms die; and, when brought into fresh nutrient solutions, are able to produce a new generation. *Spore-formation* is most frequently *endogenous*—that is, the spore arises inside the cells (particularly in bacilli), and is developed out of the cell-protoplasm, in which there appears a small granule which grows into an oblong or round, highly refractive, sharply-contoured body always remaining smaller than the mother-cell. After the death of the latter the spore is set free.

In old cultures bacteria show **degeneration-forms,** which are distorted, and stain poorly and irregularly.

As non-chlorophyllaceous plants, the schizomycetes are restricted in their **nutrition** to ready-formed **organic substances** which are soluble in water, and which are supplied to them in an abundance of **water.** In addition they need **various mineral substances,** especially sulphur, phosphorus, potassium or rubidium, or cæsium and calcium (or magnesium, barium, or strontium). Changes in the conditions of nutrition may modify the form and dimension of bacteria and also their vital properties.

Some of the fission-fungi are restricted for their food-supply to dead organisms or to solutions of organic matter, and are, therefore, classed as **saprophytes;** others are able to take their nutrition from living animals or plants, and live as **parasites.**

Free **oxygen** is necessary for the development of many bacteria; others can dispense with it as long as they are under favorable conditions of nutrition in other respects; others develop only in the absence of oxygen. The first are designated *obligate aërobes,* the second *facultative anaërobes,* the third *obligate anaërobes.*

The pathogenic bacteria are facultative or obligate anaërobes.

Carbon dioxide has no influence on the development of many bacteria, for example, on the typhoid-bacillus and Friedländer's pneumobacillus. On others, it has an inhibitory action, for example, on *Bacillus indicus, Proteus vulgaris, Bacillus phosphorescens*, the bacilli of anthrax and cholera, the pus-cocci, and others. The bacilli of anthrax, Asiatic cholera, and of rabbit septicæmia die in a few hours in artificial Seltzer water, but anthrax-spores remain alive in it indefinitely.

Light has an injurious or destructive influence on many forms of bacteria, and it is therefore possible to disinfect, by means of strong light, water which is infected. The virulence of the bacillus of anthrax may

be lessened by exposure to sunlight. When exposed to the direct rays of the sun anthrax bacilli die in twenty-four to thirty hours, the spores survive as long as six to eight weeks. According to Geisler the green, violet, and ultra-violet rays are particularly active. According to Rieder bacteria may be destroyed by the Roentgen-rays.

The **temperature** of the surrounding medium acts on bacteria in such a way that when it falls the life-processes of the organisms become weaker and slower, and finally cease entirely, whereas with elevation of temperature they rise to a certain maximum, and at a slight increase above this suddenly cease; higher temperatures kill the fungi. The maximum of permissible temperature lies at a different height for different fungi, and is dependent also on the character of the nutrient substance. There are forms of bacteria which grow well at a temperature of 55° C. or higher.

A low temperature checks development in all varieties; they fall into a state of immobility, but do not die even at great degrees of cold. The immobility due to cold occurs at different temperatures with different varieties. The most favorable temperature for development lies between 30° and 40° C. for the anthrax bacillus; at temperatures above 44° and below 15° C. its development ceases. Many bacilli form spores only at high temperatures.

Boiling water and *steam* at 100° C. kill all bacteria and bacterial spores, if allowed to act for some time. In dry air bacteria and their spores withstand higher temperatures, so that a temperature of 140° C. for three hours is necessary to kill the latter. Many bacteria are killed at a temperature of 60° to 70° C., provided it is kept up for a long time.

Anthrax-spores die in boiling water in two hours, in confined steam in ten minutes. The action of steam at 105° C. for ten minutes kills all spores. *Live steam* kills all spores in ten to fifteen minutes, and penetrates well into objects to be disinfected.

If fission-fungi find themselves in a suitable medium, their multiplication can be brought to a standstill, since the fluid may contain **substances which hinder the growth of bacteria** or **even kill them.** This effect is produced by many substances (sublimate, lysol, carbolic acid, iodine, formaldehyde, etc.) — even in comparatively great dilution. Other substances act injuriously on bacteria only when in stronger concentration. The point at which multiplication is hindered is reached at a greater dilution than that at which the bacteria are killed. Spores are much more resistant than the vegetative forms.

The growth and multiplication of bacteria also cease with **insufficient amount of water.** The fact that fruits preserved in sugar do not ferment and that salted and dried meats do not putrefy depends on this fact. Food-stuffs can be preserved through the removal of water and by the addition of substances which are dissolved in the tissue-fluids and in this way increase the proportion of the same in solid contents. The limit at which the fission-fungi and yeast-fungi cease to develop is reached at a much higher degree of humidity than for the moulds.

If a nutrient fluid contains other lower fungi besides bacteria there often takes place **competition between the different micro-organisms;** and fission-fungi, yeasts, and moulds may crowd one another out. Likewise reciprocal **crowding between the bacteria themselves** may occur. For example, cocci may be crowded out and destroyed by bacilli, or one form of bacillus by another. This would appear to happen when the composition or the temperature of the nutrient medium is more favorable

to one form than to the other; or when one form of bacteria produces substances which act injuriously on the other, or when one form grows more rapidly than the other, and thereby deprives its competitor of necessary food-supply.

According to investigations by Pasteur, Emmerich, Bouchard, Woodhead, Blagovestchensky, and others, the antagonism between many forms of bacteria is shown in inoculation experiments on animals. By simultaneous inoculation with different bacteria the development of a pathogenic bacterium in the body of a susceptible animal may be hindered. For example, the development of anthrax bacilli may be hindered by simultaneous inoculation with erysipelas-cocci (Emmerich) or with the *Bacillus pyocyaneus* (Bouchard).

The question as to whether the bacterial cell contains a **nucleus** has been a subject of much discussion. *A. Fischer* denies it, while *Bütschli, Schottelius, Ziemann, Zettnow, Nakanishi,* and *Feinberg* are inclined to favor the affirmative view. According to *Zettnow,* the bacterial cell contains chromatin or nuclear substance mixed with the entoplasm; while the covering of the cell, or ectoplasm, does not contain chromatin. According to the investigations of *Ziemann, Zettnow,* and *Feinberg,* it is possible through staining with a mixture of methylene-blue and eosin. (*Romanowski*-stain) to demonstrate within the majority of bacteria a "nuclear substance" or "chromatin" (*Ziemann, Zettnow*) or a "nucleus" (*Feinberg*) — that is, there may be demonstrated within the bacteria structures of varying size which stain red like the nuclei of malarial plasmodia (*Romanowski*) or of other protozoa or of tissue-cells, while the cell-plasma takes a blue stain. According to *Nakanishi,* circumscribed nuclei are found in young forms.

The *Romanowski*-stain is a mixture of methylene-blue and eosin, whereby a red dye contained in methylene-blue (*Rosin, Berl. klin. Wochen.,* 1899; *Nocht, Cbl. f. Bakt.,* 1899) is precipitated. *Zettnow's* formula is as follows: 50 c.c. of a one-per-cent. solution of a *Höchst* methylene-blue is treated with 3-4 c.c. of a five-per-cent. solution of soda. To 2 c.c. of this there is added drop by drop while shaking 1 c.c. of one-per-cent. solution of *Höchst* eosin BA. Stain five minutes on cover-glass and examine in water.

According to *Nägeli, Zopf,* and others, many fission-fungi possess a membrane of cellulose or of a carbohydrate closely related to cellulose. Certain bacteria (*red sulphur bacteria*) combine within their cell-substance coloring-matter; others (*Bacillus amylobacter, Spirillum amyloferum*) give at certain stages of their development the starch reaction with iodin.

Babes and *Ernst.* by means of special staining methods with *Löffler's* methylene-blue, hæmatoxylin, and *Platner's* nuclear black, have demonstrated the presence of *granules within different forms of bacteria,* which according to their behavior probably stand in some relation to the processes of division and spore-formation. *Ernst* designated the appearances seen by him as *sporogenous granules,* since he was able in certain bacteria to demonstrate their transition into spores; he is inclined to regard them as of the nature of cell-nuclei, a view which *Bütschli* also favors. *Bunge* regards the granules described by *Ernst* as cell-granules which have nothing to do with spore-formation, and describes other granules, which stain with *Löffler's* methylene-blue, as the forerunners of spores. *Marx* and *Woithe* regard the *Babes-Ernst* granules as not being nuclei in the ordinary sense of the word, but as products of the maximal condensation of the euchromatic substance of the cells, which are a sign of the highest intensity of vitality on the part of the cell. *Wagner,* on the contrary, holds that certain bodies, which he has observed in typhoid- and colon-bacilli, are nuclei.

According to *Nakanishi,* the spores form (in anthrax- and hay-bacilli) by concentration of the chromophile substance about the nucleus, while the remaining portion of the protoplasm becomes clear; a membrane is then formed about the chromatin body, it takes on a fat-like shine, and loses its power to take stains (methylene-blue BB).

The bacteria are able to take the **carbon** necessary for their growth from most of the carbon compounds which are soluble in water. They can also derive their carbon from dilute solutions of substances which, in greater concentration, are injurious to them — for example, from benzoic acid, alcohol, salicylic acid, phenol, etc.

Their **nitrogen** is derived from *albuminous matter;* further, from those compounds designated as *amins* (methyl-, ethyl-, propylamin), amido-acids (asparagin, leucin) and *amides* (oxamide, urea), as well as from the *ammonia salts* and also from *nitrates.* The albuminates, previous to their assimilation, are changed into peptone by means of a ferment given off from the bacteria. Free nitrogen cannot be assimilated as such. Nitrogenous and non-nitrogenous compounds are not only assimilable as such, but also in combination. The fission-fungi are able to take nitrogen from ammonia and nitric acid only in the presence of organic carbon compounds.

Sulphur, according to *Nägeli,* is essential to the schizomycetes, and they take it from sulphates, sulphites, and hyposulphites. The other *mineral substances* mentioned above are derived from various salts. If in the case of an abundance of nutrient material there is too little water present, all further growth ceases; yet many of the fission-fungi are able to dispense with water temporarily. Spores suffer little from drying.

Many bacteria are sensitive to **acids,** so that even a slight dgree of acidity hinders their growth (for example, anthrax bacilli and the Fränkel-Weichselbaum pneumococcus). Others are able to grow with a moderate amount of acid in the nutrient fluid. As a general rule they are especially sensitive to mineral acids, but the presence of a large amount of citric, butyric, acetic and lactic acids also hinders their multiplication. In this connection belongs the fact that the products of decomposition caused by the fermentative action of the fungi are at a certain degree of concentration harmful to the development of the fungus, and finally stop its growth entirely. Thus, in butyric-acid and lactic-acid fermentation the amount of butyric or lactic acid gradually formed finally checks the multiplication of the fungus. A similar result occurs in the bacterial putrefaction of albumin, since the products of the same, such as phenol, indol, skatol, phenylacetic acid, phenylproprionic acid, etc., hinder the further development of the bacteria. To alkalies the fission-fungi are less sensitive, and many can bear a rather high degree of alkalinity in the nutrient fluid, but there also exist forms which do not thrive in alkaline fluids (acetic-acid fungus).

According to the investigations of *Pfeffer* and *Ali-Cohen,* many motile bacteria show **chemotactic properties** — that is, they are attracted or repelled by certain chemical substances dissolved in water. Bacteria swimming about in fluids collect, therefore, at places where there are chemical substances which attract; for example, typhoid-bacilli and cholera-spirilla are attracted by potato-juice (*Ali-Cohen*). Potassium salts, peptone, and dextrin likewise attract, but the individual forms of bacteria behave differently toward these substances (*Pfeffer*). Free acids, alkalies, and alcohol have a repelling action.

§ 149. **The growth and multiplication of fission-fungi give rise to chemical transformations of the nutrient material,** brought about through *ferments produced by the bacteria,* and through *metabolic processes occurring in the cells themselves.*

Among **ferments** or **enzymes** are to be mentioned the *proteolytic* or *albumin-dissolving enzymes* (*bacteriotrypsins*) which bring about solution of the albuminous bodies and cause disintegration of the peptone-molecule. Further, bacteria give rise to *diastatic ferments* which convert starch into sugar, also to *inverting ferments* which transform cane-sugar (disaccharid) into grape-sugar (monosaccharid).

The **chemical results of bacterial metabolism,** brought about by the vital activities of fission-fungi aided by the enzymes produced by them, consist of decomposition of complex organic compounds. By many authors all these processes are designated **fermentations,** while others (Lehmann) speak of fermentation only when a fission-fungus breaks down a given food-material with especial ease, thereby giving rise to one or more products in marked quantity, in association with or in place of its other metabolic products. Other authors narrow the term fermentation to the decomposition of carbohydrates.

In the **decompositions caused by fission-fungi different products** are formed, according to the composition of the nutrient material and the

character of the fission-fungus. For the production of fermentation fermentable material is necessary. Many fungi are able to cause fermentation in the presence as well as in the absence of oxygen, while to some of them lack of oxygen is necessary.

Among the **products of bacteria** of importance to the physician are those which **have a poisonous action and cause tissue-changes,** particularly those described as *ptomaïns, toxins,* and *endotoxins.*

The **ptomaïns** are basic, crystallizable, nitrogenous products of the bacterial decomposition of albumin; they are also known as *putrefactive alkaloids* or *cadaveric alkaloids.* They show *poisonous properties.* The best known are sepsin, putrescin (dimethylethylendiamin), cadaverin (pentamethylendiamin), collidin (pyridine derivative), peptotoxin, neuridin, neurin, cholin, gadinin, and substances resembling muscarin.

The **true toxins** are specific bacterial poisons produced by pathogenic bacteria and are secreted by the latter, giving rise to the severe symptoms in diphtheria, tetanus, and sausage poisoning. The **endotoxins** are substances clinging to the bacterial cells that also have a poisonous action. In the bacterial cell there also occur **bacterial proteins** which give rise to local tissue-necrosis and inflammation. The significance of these substances in the infectious diseases has already been mentioned in § 11.

Among other **decompositions produced by bacteria** the following are worthy of note: the formation of lactic, formic, acetic, propionic and butyric acid, alcohol and carbonic acid from sugar; the formation of acids (acetic, butyric, propionic, valerianic, succinic, formic, and carbonic) from alcohol and organic acids; the formation of indol, skatol, phenol, cresol, pyrocatechin, hydrochinon, hydroparacumaric acid, and paroxyphenylactic acid (*von Nencki, Salkowski, Brieger*), and finally hydrogen sulphide, ammonia, carbonic acid, and water from albumin; the formation of ammonium carbonate from urea; the transformation of nitrous and nitric acids into free nitrogen; the reduction of nitrates to nitrites and to ammonia, etc. Finally, there are bacteria living in the soil — the nitro-bacteria — which are able to form nitrous and nitric acids from ammonia (*Winogradsky*).

Along with the nitrification of nitrogen there occurs decomposition of earthy alkali carbonates, as shown by the fact that the nitrobacteria are able in the presence of organic carbon compounds to derive *from the carbonates the carbon necessary to the building-up of cells.* There takes place, therefore, through the vital activity of these organisms, synthesis of organic out of inorganic substances.

Under the influence of the fission-fungi there are formed *bitter, sharp, nauseating substances* (bitter milk). Further, bacteria occasionally produce *pigments* of red, yellow, green, blue, or violet color. For example, *Bacillus prodigiosus* produces a blood-red coating on bread (bleeding bread); bandages and pus take on a bluish-green color as the result of the presence of *Bacillus pyocyaneus.* In many cultures there is formed fluorescent coloring-matter.

The *phosphorescence* not infrequently seen on decomposing sea-fish depends on bacterial products of decomposition, as has been shown by *Pflüger,* and appears when there is active multiplication of the bacteria.

2. General Considerations Concerning the Pathogenic Schizomycetes and Their Behavior in the Human Organism.

§ 150. Among the schizomycetes there are numerous species which are capable of causing disease-processes in the human organism, and are therefore called **pathogenic schizomycetes.** The bacteria concerned must possess properties enabling them to multiply in the tissues of the living human body. They must therefore find in the tissues suitable nutrient material, and in the body-temperature the warmth necessary to their growth. The tissues, moreover, must not contain substances which are a hindrance to growth (cf. § 31).

If pathogenic fission-fungi succeed in growing in the tissues of the body, if **infection** takes place (cf. § 11), their action is characterized *at the point of multiplication,* by *tissue-degenerations, necrosis, inflammation,* and *new-growths of tissue,* while at the same time the *toxins* produced by them cause *manifestations of poisoning.*

In individual cases the pathological processes vary greatly, in that the distribution of the bacteria, their local action, and the production of poisons, differ with different forms of bacteria.

With many the *local action* on tissue is the most prominent characteristic, with others the *general intoxication.* Many bacteria *confine themselves to the region in which they have gained entrance; others advance uninterruptedly on the surrounding tissues;* still others are carried by the blood and lymph streams and lead to the formation of *metastatic foci,* and, finally, others *increase in the blood.*

If spread of bacteria takes place through the blood, the bacteria *may pass from the mother to the fœtus* during pregnancy, since the placenta forms no certain filter against pathogenic bacteria. This has been demonstrated, for example, in the case of anthrax-bacilli, bacilli of symptomatic anthrax, glanders-bacilli, spirilla of relapsing fever, typhoid-bacilli, the pneumococcus, and the spirochete of syphilis. Changes in the placenta, such as hæmorrhage, loss of epithelium, and alterations of vessel-walls, favor the passage of bacteria.

Bacteria which multiply in the human body *die out in many cases in a short time;* and the disease produced by them proceeds to *recovery* (cf. § 31). Nevertheless, it not infrequently happens that *they are preserved for a long time in the body,* and *excite continuous disease,* or remain in a condition of inactivity, so that no pathological processes are recognizable until, *after a period of latency, active reproduction again takes place and manifestations of disease show themselves anew.*

Not infrequently **secondary infection** associates itself with infection already existing. The relation between the two is either that the second follows the first accidentally, or that through the first infection the soil is prepared for the second (cf. § 11).

Finally, there not infrequently occur **double infections,** in that two or more forms of bacteria develop coincidently in the tissues, and produce their characteristic injurious influence on the latter.

Each pathogenic fission-fungus has a **specific action** on the tissues of the human organism; but *different species may exert a similar action.* For example, there are various bacteria capable of producing suppuration. Only in a certain proportion of cases do the tissue-changes show such characteristics that from these the species of the pathogenic fission-fungus can be recognized with certainty.

Further, it has been demonstrated that **pathogenic properties of bacteria are by no means constant;** on the contrary, their virulence varies, so that bacteria, which cause severe infections may become changed (weakened) through external influences, so that they lose their power of causing disease, or cause only mild forms. This peculiarity is of great practical importance. It explains to a certain extent why a given infection does not always run the same course, and, moreover, why with severe attacks light ones also occur. On the other hand, it affords the possibility of obtaining *material for inoculation* from attenuated cultures of bacteria, by means of which mild grades of infection or intoxication

can be produced, which are able to protect the organism from severe infections or to bring about the cure of an infection already acquired (cf. § 32).

Weakening of the pathogenic properties of a fission-fungus can be brought about through the action on cultures of high temperatures, oxygen, light, or antiseptic substances, as well as by cultivation of the fungus in the body of a less susceptible animal. In some forms it is only necessary to cultivate the bacteria for some time on artificial media (diplococcus of pneumonia), or to expose the culture to the air (bacillus of chicken-cholera), in order to bring about attenuation. If it is desired to preserve the virulence of the pneumococcus, it is necessary, from time to time, to pass the bacteria cultivated on artificial media through rabbits, which are very susceptible. The glanders-bacilli, tubercle-bacilli, and the cholera-spirilla lose virulence when cultivated uninterruptedly on artificial media. The streptococcus of erysipelas becomes so attenuated through continued cultivation in bouillon that it is no longer capable of killing even mice.

If the presence of bacteria be suspected in tissue-fluid or in the tissue-parenchyma, their demonstration may first be attempted by means of **microscopic investigation**. Occasionally this is successful by the mere examination of a drop of the suspected fluid or of a smear-preparation of the tissue-juice diluted with salt-solution or distilled water. In other cases it is necessary to employ *staining methods*, in which case cover-glass smears of the fluid are made and allowed to dry. The smear is then fixed by passing through the flame, and after cooling is stained. For this purpose methylene-blue is preferably employed, a preparation of one-per-cent. methylene-blue solution in 1-to-10,000 solution of caustic potash. Water solutions of fuchsin and methyl-violet are also used. For many bacteria there are employed special staining methods, in which ordinarily the preparations are heavily overstained with a solution of gentian-violet or fuchsin in aniline water, or with a water solution of methyl-violet, the excess of stain then being removed by means of weak acids or by iodine and alcohol (*Gram's* method). In this way it is often brought about that the bacteria alone remain stained, often certain forms of bacteria only.

When it is desired to demonstrate the presence of bacteria in tissues, small portions of tissue are hardened in formalin or in absolute alcohol, and are then cut into the *thinnest possible sections, which are stained by appropriate methods*. Here again the methods most frequently employed are those mentioned above: gentian-violet, methyl-violet, and fuchsin. Good objectives are necessary for the microscopic examination; if possible, oil-immersion lenses and illumination with substage condenser should be employed.

If through any method the presence of **bacteria** in tissue has been demonstrated, the attempt is next made to **cultivate** them. For this purpose the methods developed by *Koch* are usually employed. These, in principle, consist in obtaining first a fluid containing the bacteria, by means of scraping or by rubbing up pieces of tissue in sterilized salt-solution. This fluid is then evenly distributed in a solution of gelatin or agar which has been liquefied by warming; and the mixture is then poured upon horizontal glass plates, solidifying as it cools. The individual bacteria or spores, thus separated from each other, develop in the nutrient medium.

By proper application of this method there are obtained in the layer of gelatin various colonies, which differ in appearance so that they may often be differentiated from each other by the naked eye alone. When sufficiently separated from one another, the individual colonies may be taken up by means of a fine platinum needle, and transferred either to boiled potato, or to a sterile gelatin plate, or streaked on the surface of the solidified nutrient fluid in a test-tube. Very often the infected needle is stuck into the solidified transparent medium contained in a test-tube.

If the culture on the gelatin plate is pure, and if the entire procedure is carried out with the necessary care and the avoidance of contamination, pure cultures may be obtained by this method. In stab-cultures, as well as in smear-cultures on pota-

toes or any other nutrient medium, special peculiarities often show themselves which make it possible for the experienced observer to recognize the form of bacteria. At times, however, it is necessary to make a thorough microscopic examination of the colonies.

An infusion of meat containing peptone and gelatin is commonly employed for making plates. It consists of a watery infusion of chopped meat, to which a definite amount of peptone and salt is added. This is neutralized with carbonate of soda, and enough gelatin is added to give a solid consistence at ordinary temperatures. For streak- and stab-cultures this same gelatin is sometimes used; at other times a jelly made of a mixture of a watery extract of meat, peptone, and agar-agar; or again blood-serum which has been coagulated by warming.

For stab-cultures the jelly is allowed to solidify within the test-tube in a perpendicular position; for streak-cultures the test-tube is kept in an oblique position until the jelly is set.

Sterilized bouillon is often used for cultures. The inoculated nutrient media are kept either at room-temperature or at higher temperatures in an incubating oven (30°-40° C.). The proper nutrient medium to be used in individual cases must be determined by experiment. Experience has shown that individual bacteria behave differently in this respect, some growing best on one, others on another medium. To the nutrient medium there are often added with advantage such substances as sugar, glycerin, urine, brain-substance, etc.

It is evident that the processes briefly described above may be modified according to the necessities of the case. For example, in those cases in which it is necessary to grow bacteria at high temperatures, the use of gelatin should be avoided and agar-agar plates should be made instead. Occasionally membranes or exudates from mucous surfaces (diphtheria) or small bits of excised tissue are placed directly into the culture-medium. In the case of many bacteria, as cholera-spirilla, the use of hanging-drop cultures is advised. In this method a drop of sterilized bouillon hangs down from the under surface of a cover-glass, and is inoculated from a previously cultivated pure culture of the fungus. The cover-glass is then placed over the excavation in a hollow ground-glass slide. Evaporation is prevented by the exclusion of the outer air from the cavity in the slide, by a rim of oil or vaseline placed beneath the edge of the cover-glass. By this method the multiplication of bacteria can be observed for a long time.

When *bacteria are sought in water,* a definite amount of suspected water is distributed in gelatin, and plate cultures are made. *Earth* is rubbed up with sterilized salt-solution; *air* is made to pass in definite amount through sterilized salt-solution; the salt-solutions thus infected are then mixed with gelatin, and from this gelatin plates are made.

The *culture of bacteria* on and in different media, accompanied by the microscopic examination of the different stages of development, *serves for more exact identification, and for the differentiation of species.* After its properties have been studied in this way, the **influence of the bacterium on the animal organism** is tested. As experimental animals, rabbits, dogs, guinea-pigs, rats, mice, and small birds are employed. The bacteria to be tested are introduced, sometimes under the skin, sometimes directly into the blood-current, sometimes by inoculation into the internal organs, sometimes by inhalation into the lungs, or by administration with the food into the intestinal canal. Bacteria can be regarded as pathogenic for a given animal when they multiply within the tissues and excite disease. If relatively large amounts are inoculated, the animal experimented on may die, even if the bacteria do not increase in its body, since the poisonous substances formed in the culture and introduced by inoculation often suffice to kill the animal.

Experience has taught that only some of the bacterial infections which occur in man, when inoculated into animals, run the same course as in man, and, indeed, only those which also occur in animals. In other cases the pathogenic fission-fungi occurring in man or in certain animals are, it is true, pathogenic for the experimental animal, but the pathological process shows another localization and another course. In a third case the experimental animals are in part or wholly immune.

Inversely, fission-fungi that are often extremely pathogenic for experimental animals are harmless for other animals or for man.

II. The Different Forms of Bacteria and the Diseases Caused by Them.

I. The Cocci, or Sphærobacteria, and the Morbid Processes Caused by Them.

(a) General Considerations Regarding the Cocci.

§ 151. The **cocci** are bacteria that occur exclusively in the form of round or oval or lanceolate cells. In their multiplication by division they often form peculiar aggregations of cells, which are designated by special names according to the character of the different forms. Since certain forms of cocci are likely to develop in definitely shaped aggregations, advantage is taken of this fact, to classify them in different **species**. It should be noted, however, that a given species does not always appear in the same form, but may vary according to nutrient conditions.

Many of the cocci multiply by division in one plane only — at right angles to the length of the cell. If the spheres resulting from division remain together for some time in the form of double spheres, and if this form appears with frequency

FIG. 382.
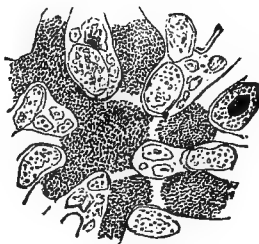
FIG. 383.

FIG. 384.

FIG. 385.

FIG. 382.—Streptococcus from a purulent peritoneal exudate of a case of puerperal peritonitis. *a*, Single cocci; *b*, diplococci; *c*, streptococci or torula-chains. × 500.

FIG. 383.—Colonies of micrococci in blood-capillaries of the liver, causing metastatic abscess-formation. From a case of pyæmia. Necrosis of liver-cells. × 400.

FIG. 384.—Cocci grouped in tetrads (merismopedia), from a softening infarct of the lung. × 500.

FIG. 385.—Sarcina ventriculi. × 400.

in any one species, it is designated **diplococcus** (Fig. 382, *b*). If, from further division of the cells in one plane, rows of cocci result, these are known as **streptococci** (Fig. 382, *c*); this term is used also as the name for a group. If the division of the cells takes place irregularly, and the cells remain in small collections or heaps, the bacteria are designated **micrococci** (Fig. 383). The name **staphylococcus** or *grape-coccus* is commonly used to indicate some of these forms. Larger collections of cells, held together by a gelatinous substance derived from the cell-membranes, are designated *zoöglœa* masses. If the masses of cocci are united into larger collections by means of a gelatinous envelope, they are spoken of as *ascococci* or *tube-cocci*.

To those cocci which remain united for a long time in a four-cell tablet (Fig. 384), the name of **tetracoccus** or **tablet-coccus** is applied. Others class such bacteria with the micrococci. The cocci that go by the name **sarcinæ** are characterized by division in three directions of space, so that compound cubical packets of spherical cells are formed from tetrads (Fig. 385).

The cocci not infrequently show a tremulous molecular motion in fluids.

The **saprophytic cocci** grow on different nutrient substrata and cause in suitable media various processes of decomposition. Many form pigments. *Micrococcus ureae* causes fermentation in urine by which ammonium carbonate is formed from urea. *Micrococcus viscosus* is the cause of the slimy fermentation of wine. The cause of the *phosphorescence of decomposing meat* was found by Pflüger to be a micrococcus that forms slimy coatings on the surface of the meat.

Of the pigment-producers the best known are *Micrococcus luteus, Micrococcus aurantiacus, Sarcina lutea, Micrococcus cyaneus* and *Micrococcus violaceus,* which, when grown on boiled eggs or potatoes, produce yellow, blue, and violet pigment, respectively.

Saprophytic cocci are found in the mouth cavity and intestine, as well as on the surface of the skin, and in the lungs.

Sarcina ventriculi (Fig. 385) occurs not infrequently in the stomach of man and animals, especially when abnormal fermentations are going
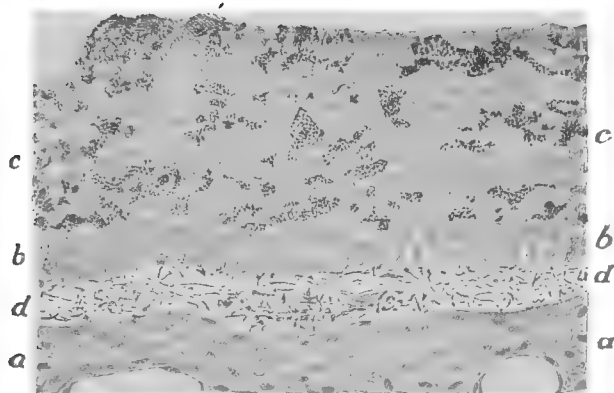
FIG. 386.—Streptococcus tracheitis in scarlet fever (alcohol, carmine, methyl-violet, iodine). *a,* Connective tissue; *b,* desquamated epithelium; *c,* membrane composed of cells and streptococci; *d,* fibrin-threads. × 300.

on. According to Falkenheim the stomach sarcines can be cultivated on gelatin, and form round, yellow colonies, which contain colorless monococci, diplococci, and tetrads, but never cubical packets. They form these, however, in neutralized hay-infusion, and their growth causes souring of the infusion. The membrane of the sarcinæ is said to consist of cellulose.

Micrococcus tetragenus is not infrequently found in human sputum, and in the mouth and throat; it may be present in tuberculous cavities, or in hæmorrhagic or gangrenous foci of the lungs. It forms tetrads (Fig. 384) whose cells are held together by a gelatinous membrane. On gelatin-plates it forms round or oval, lemon-yellow colonies. It is pathogenic for white mice and guinea-pigs, to a less extent for rabbits, and, when injected subcutaneously, excites purulent inflammations in the mouse, often septicæmia. Intratracheal injections may give rise to inflammations of the respiratory passages and lungs.

The **pathogenic cocci** cause acute inflammations which usually heal after death of the bacteria; but it not infrequently happens that cocci may remain in the body for a long time and give rise to chronic processes.

28

(b) The Pathogenic Cocci.

§ 152. The **Streptococcus pyogenes** is a coccus which, in multiplying, forms *double spheres* and *chains of spheres* (Fig. 382) of different lengths, containing from four to twelve or more cells. This chain-formation comes to especially full development when the streptococcus is growing in fluids — in nutrient bouillon or fluid exudates — but is also seen when growing in tissues.

The cocci stain well by Gram's method, are facultative anaërobes, grow best at 37° C., and form small whitish colonies on gelatin and agar.

Streptococcus pyogenes causes in man **inflammations,** *which usually, though not always,* assume a **purulent character.** Occasionally it is found on normal mucous membranes, for example, in the upper air-passages, or in the vagina and cervix uteri; it may be assumed in such cases that its virulence is slight, or that the mucous membranes offer successful resistance to its entrance into the tissues.

FIG. 387.—Streptococcus pyogenes from a phlegmonous focus of the stomach (alcohol, carmine, methyl-violet, iodine). *a,* Leucocytes; *b,* leucocytes containing streptococci; *c,* free streptococci. × 500.

Infection with streptococci may occur either in healthy individuals, or in those who have received some injury, or as an accompaniment or sequel of other infections, particularly scarlet fever, smallpox, diphtheria, and pulmonary tuberculosis.

FIG. 388.—*Streptococcus erysipelatis* (*a*) inside a lymph-vessel (*b*), in part composed of thickly crowded spheres, in part of torula-chains (alcohol, gentian-violet); *c,* neighborhood of lymph-vessel, with pale, non-staining nuclei; *d,* vein; *e,* perivenous cellular infiltration of tissue; *f,* accumulation of cells in the lymph-vessel. Section of rabbit's ear two days after inoculation with erysipelas-cocci. × 225.

If the streptococcus multiplies on the *surface of mucous membranes* — for example, of the respiratory tract (Fig. 386) — it excites *inflammation,* which may bear the character of *desquamative* or *purulent catarrh* (*c*), or of a *croupous exudation* (*d*). If it penetrates the connective tissues of the submucosa, it causes inflammations which are *phlegmonous* in character — i.e., a more or less quickly spreading, seropurulent, or purulent, or fibrinopurulent, or serofibrinous inflammation, which may lead to suppuration and abscess-formation. In the exudate the cocci may be found free (Fig. 387, *c*), or inclosed in cells (*b*).

The *multiplication of streptococci in the stratum germinativum* of the skin leads to necrosis of epithelium and the formation *of purulent vesicles* or *blebs.*

If the streptococcus spreads in the *corium,* into which it penetrates through small wounds of the skin, it utilizes the lymph-spaces and lymph-

vessels (Figs. 388, *a;* 389, *h, i;* 390, *c*) as pathways and as places for the development of colonies, causing more or less severe inflammation, characterized macroscopically by advancing redness and swelling of the skin known as *erysipelas.* To the external appearance there corresponds more or less severe serous and cellular infiltration (Figs. 388, *d, e, f;* 389, *m;* 392,*c*), and often fibrinocellular exudation (Fig. 389, *m₁*). The infection of the lymph-vessels in erysipelas involves at times the superficial layers of the cutis (Fig. 389), at other times the deeper layers (Fig. 390, *c*). In the latter case the erysipelatous process becomes phlegmonous. With infection of the deeper layers streptococci may spread on the surface of the epithelium — that is, beneath the horny layer (Fig. 390, *g*), and cause loosening of the epithelial cells and desquamation of the horny layer (*f*). In severe infection with virulent streptococci the process may go on to
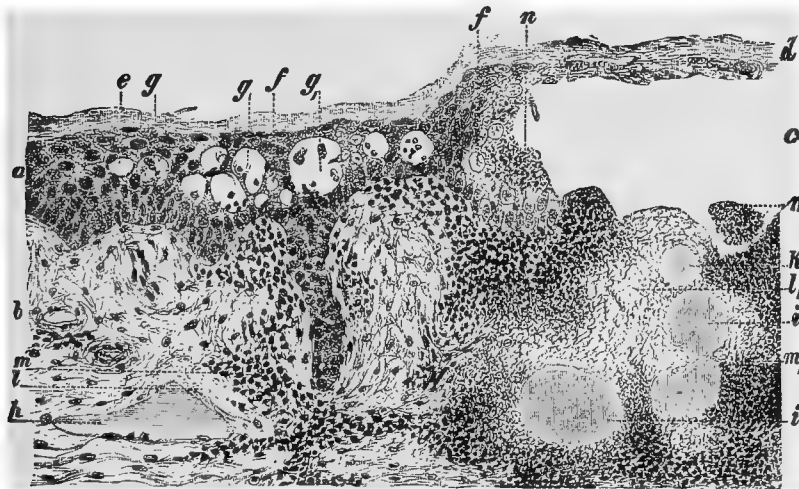
Fig. 389.—Section of the skin in erysipelas bullosum (alcohol, alum-carmine). *a,* Epidermis; *b,* corium; *c,* vesicle; *d,* covering of vesicle; *e,* epithelial cells containing vacuoles; *f,* swollen cells with swollen nuclei; *g, g₁,* cavity caused by the liquefaction of epithelial cells, and containing fragments of epithelium and pus-corpuscles; *h,* lymph-vessel, partly filled with streptococci; *i,* lymph-vessel filled full of streptococci; *k,* colony of streptococci in the tissue; *l, l₁,* necrotic tissue; *m,* cellular, *m₁,* fibrinocellular infiltration; *n,* fibrinocellular exudate in the vesicle. × 60.

liquefaction of epithelium (Fig. 389, *e, f, g, g₁'*), and to the formation of vesicles (*c,* erysipelas bullosum), or to necrosis and gangrene of the corium (*l, l₁,* erysipelas gangrænosum), or to suppuration.

In the *subcutaneous tissue* the spread and multiplication of the cocci (Fig. 391, *c*) lead to progressive seropurulent (*d*) and fibrinopurulent inflammation, often with subsequent suppuration. Such forms of infection are known as *phlegmons.*

If the *muscles become involved in a phlegmonous process,* the streptococci increase and spread (Fig. 392, *a*) in the connective tissue of the perimysium internum, and may penetrate the sarcolemma-tubes. Here also the consequences of infection are more or less severe inflammations leading to *suppuration.*

Bronchogenous infection of the lungs causes purulent, or croupous, or hæmorrhagic exudations into the alveoli.

Should bone become involved from the skin or mucous membrane — for example, from the middle ear — the cocci may increase in the marrow

(Fig. 393, *a, b*) and give rise to necrosis, and later to purulent inflammation of neighboring tissues.

Streptococcus infection may terminate, sooner or later, in that opposing forces restrict the further spread of the bacteria, and destroy them. Not infrequently, however, infection progresses up to the time of death.

If streptococci break into the lymph- and blood-vessels, *metastases* are formed, and distant organs are involved. *Infection of the lungs* leads easily to infection of the *pleura*. Infection of the *female genital tract*, during delivery or the puerperium, leads often to infection of the *peritoneum* by the lymphatics. Infection of the *serous membranes* is
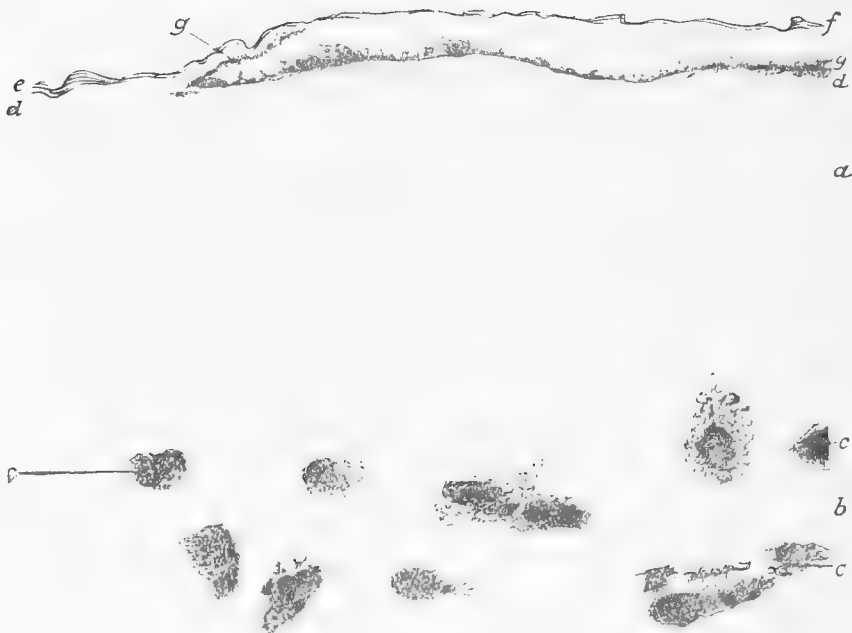
FIG. 390.—Erysipelas of the head in a child of one month of age (bacterial staining, carmine). *a,* Cutis with hair-follicles; *b,* subcutis; *c,* lymph-vessel with streptococci and inflamed surrounding area; *d,* rete Malpighii; *e, f,* horny layer; *g,* streptococci lying upon the rete Malpighii. × 45.

usually associated with seropurulent, or fibrinopurulent exudation, the streptococci developing luxuriantly in the exudate, and forming long chains. In infection of the blood, the streptococci do not increase in the circulating blood, but at points where they come to rest; in the small capillaries of the lungs, heart, liver, kidneys, spleen, bone-marrow, joints, etc., or on the valves of the heart. At the point of increase there is likewise produced inflammation, which bears the same general character as the primary inflammation, but is less severe and more circumscribed.

Hæmatogenous streptococcus-infection of the lung leads to the formation of inflammatory foci (Fig. 394, *a*), which for the greater part show central suppuration. Collections of streptococci on the *surface of the endocardium* of the valves or of the heart wall (Fig. 395, *a*) lead to superficial necrosis and to the formation of coagula (*b*), collections of leucocytes (*b₁*) and proliferations of granulation tissue (*c, d*). Deeper infection with streptococci causes extensive necrosis accompanied by in-

flammation of the surrounding tissues. If streptococci are carried by the blood-stream into the coronary arteries, there are produced in the heart-muscle inflammatory foci, usually purulent in character.

If the cocci pass to a blood-vessel of the skin or subcutaneous tissue, they may increase to such an extent that they form casts of the capillaries (Fig. 396, c). As the result of surrounding hyperæmia there are produced in the skin red spots and swellings, and eventually purulent foci. In the *kidneys*, in whose vessels there often occurs an extraordinary multiplication of streptococci (Fig. 397, a, b), there arise grayish-yellow circum-

Fig. 391.—Beginning streptococcus phlegmon on the trunk, after phlegmon of the arm (formalin, carmine, methyl-violet). a, b, Skin; c, streptococci in the subcutaneous connective tissue; d, beginning collection of leucocytes. × 15.

scribed areas of discoloration, which are dependent on collection of bacteria, local anæmia, necrosis, and often serofibrinous exudation (d). Later, yellow discolorations and softening of tissue appear, corresponding to foci of suppuration. Similar changes may be demonstrated in other organs.

The *danger of streptococcus infection* depends on *progressive local changes* and the *formation of metastases,* and on the accompanying *intoxication,* which finds expression in fever and severe general symptoms. If the symptoms of intoxication are prominent the condition is designated **septicæmia.** Metastatic suppuration leads to the form of disease designated **pyæmia.** A combination of both conditions is known as **septico-pyæmia.**

The course of streptococcus infection, as well as the mode of entrance of the cocci into the body, can usually be recognized, since the infection ordinarily starts in injured skin or from penetrating wounds, from the mucosa of the digestive and respiratory tracts, or from the genital apparatus as the result of childbirth. **Cryptogenic infection** is, however, not rare; in such cases the first symptoms recognizable clinically are those dependent on disease of an internal organ, so that it appears as if the infection were primary in this organ.

The individual foci in streptococcus infection may present different degrees of inflammation; this is dependent on the virulence of the bacteria, on individual differences of the infected persons, on the seat of the infection, and on the influence of preceding or accompanying condi-
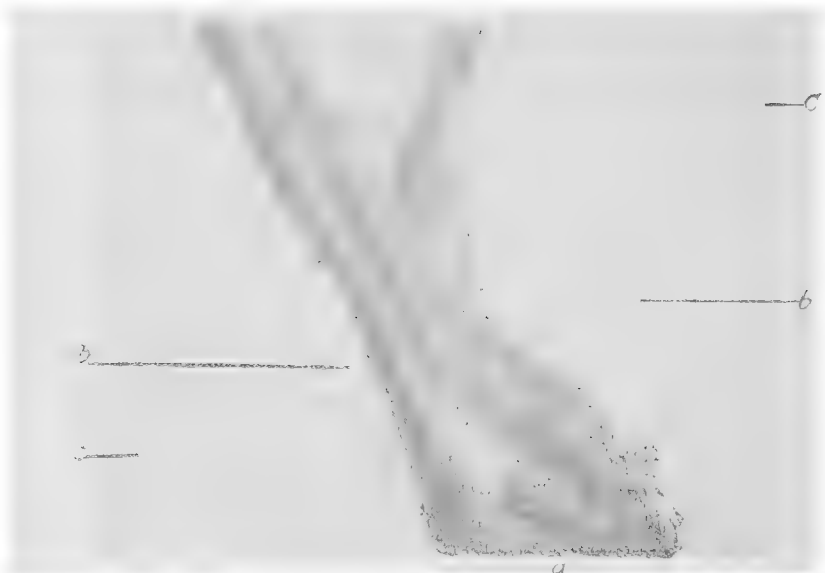
Fig. 392.—Streptococcus phlegmon in muscle. (Alcohol, Weigert's stain.) *a*, Masses of streptococci; *b*, leucocyte infiltration; *c*, transverse section of muscle-fibres. × 100.

tions. In respect of this last factor it may be noted that many infectious diseases (diphtheria, scarlatina, smallpox, tuberculosis, typhoid fever, influenza) which lower resistance increase the predisposition to streptococcus infection. In the growth of streptococci on the surface of the endocardium, the inflammation often bears a pronounced proliferative character (Fig. 395, *d*, *c*). In hæmatogenous streptococcus-dermatitis (Fig. 396) the process may cease with the formation of red spots. Phlegmons, although they usually pursue a rapid course and lead in a short time to necrosis and suppuration, may also have a chronic course, particularly in the neck, and are characterized by progressive swelling and induration of the affected area, so that the affection is familiarly designated "*wooden phlegmon.*" Fever may be absent. The process consists of progressive proliferation of granulation tissue and new-formation of connective tissue due to streptococci (or staphylococci), while suppuration is absent or confined to circumscribed areas.

The biological characteristics of *Streptococcus pyogenes* are variable; this is well shown both in its behavior as a disease-producing agent and in cultures of streptococci taken from different cases. Consequently an effort has been made to divide streptococci into different species, in particular has the streptococcus which causes erysipelas been regarded as a distinct form — the *Streptococcus erysipelatis*. Further, according to the place in which the streptococcus was found, it was formerly customary to speak of *Streptococcus puerperalis*, *Str. articulorum*, *Str. scarlatinosus*; or, according to the manner of growth, of *Str. longus* and *Str. brevis*, etc. These characteristics are, however, not sufficient to form a basis for the separation of streptococci into different species; and it appears more correct, or at least more expedient, to consider all the chain-forming streptococci as one species, which appears in many varieties. According to *Howard* and *Perkins* (*Jour. of Med. Research*, 1901) there is a small group of pathogenic capsulated streptococci characterized by the viscidity of their growth and by the formation of gelatinous exudations in animals. For this group they propose the name of *Streptococcus mucosus*.
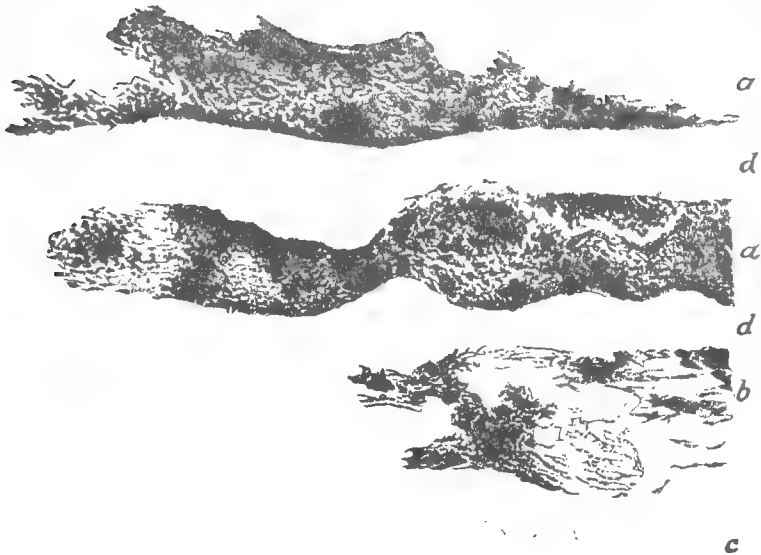
Fig. 393.—Streptococcus infection of the petrous portion of the temporal bone, from a child of eight months of age (formalin, nitric-acid decalcification, carmine, methyl-violet). *a*, Medullary spaces completely filled with streptococci; *b*, beginning invasion by streptococci; *c*, bone marrow; *d*, trabeculæ of bone. × 300.

In diphtheria and scarlet fever, streptococcus infections of the throat and air-passages are extremely common, particularly in the first-named, so that many authors are inclined to assign to the streptococcus a co-ordinate position with the diphtheria-bacillus in the causation of diphtheria — the diphtheria-bacilli predominating in the lighter forms of infection, the streptococci in the more severe. Pure streptococcus infections may present the same picture as that produced by *Loeffler's* bacillus. If both forms of bacteria are present, their effects may be combined; perhaps the presence of streptococci increases the virulence of diphtheria-bacilli.

The *Streptococcus pyogenes* is especially pathogenic for mice and rabbits (less so for dogs and rats); but its virulence varies greatly, and rapidly decreases in cultures grown on ordinary media. Its virulence is retained for a relatively long time (*Marmorek*) in cultures of the cocci in human- or in horse-serum (serum two parts, bouillon one part), or in a mixture of bouillon and ascitic fluid.

The **nature of the poisons produced by streptococci** is not known. It has been definitely determined that filtered cultures sterilized at 65–70° C. contain poisons; but it is not yet known whether this poison, like the toxin of the diphtheria-bacillus, produces an antitoxin.

According to *Simon* there can be distinguished an intracellular weakly virulent poison and a toxin excreted by the streptococcus. The latter, however, is produced only under certain conditions, for example, under the influence of the bactericidal juices of the animal body. Under certain conditions the streptococcus can also produce hæmolysin.

Numerous investigators (*Neufeld, Rimpau, Tavel, Menzer, Aronson, Marmorek, Moser,* and others) have attempted to immunize animals against streptococci and to produce an antistreptococcus serum, and the sera thus obtained have been used in the treatment of streptococcus affections in man. At present it is not possible to judge as to the therapeutic value of these procedures.
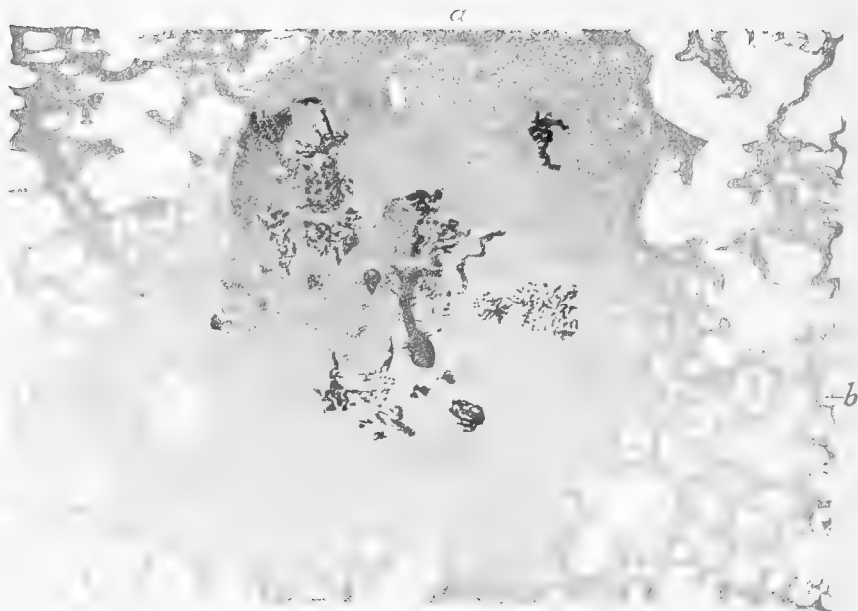
FIG. 394.—Metastatic hæmatogenous streptococcus pneumonia, after angina (alcohol, alum-carmine, methyl-violet, iodine). *a*, Pneumonic focus with (blue) streptococci; *b*, slightly inflamed lung tissue about the focus. × 80.

§ 153. The **Diplococcus pneumoniæ, Streptococcus lanceolatus,** or **Diplococcus lanceolatus,** familiarly known as the *Pneumococcus,* is of frequent occurrence. It forms spherical, oval, and lanceolate cocci (Fig. 398, *a*), which in the human body are usually surrounded by a capsule, and are grouped in pairs (*b, d*), or more rarely in chains of such pairs (*c*), or in large colonies (*d*).

The pneumococcus stains well with fuchsin and with gentian violet, and by these stains the capsule may be demonstrated in smear-preparations. The cocci are also stained by Gram's method.

The cocci are facultative anaërobes. They will not grow on gelatin at ordinary room-temperature, but do so on slightly alkaline blood-serum-gelatin, on agar and in bouillon, at a temperature above 22° C., and best at the temperature of the body. They form on the surface of the medium a delicate, translucent, glistening culture, which suggests the dew-like deposit of moisture on glass (Fränkel) ; and consists of diplococci and chain-cocci without capsules. The growth is, however, scanty; and easily dies out. Upon potatoes cultures do not thrive.

The Diplococcus pneumoniæ is in a great number of cases (according to Weichselbaum in seventy-one per cent.) the cause of *croupous pneumonia,* in which the lung is the seat of an acute inflammation ushered in by congestive hyperæmia (Fig. 399, *a*). In the course of the disease the alveoli over large areas become filled with coagulated exudate consisting of desquamated epithelium, leucocytes, red blood-cells, serous fluid and fibrin (Fig. 176). In favorable cases the exudate becomes liquefied and absorbed. As has been shown by numerous observations, the Diplococcus
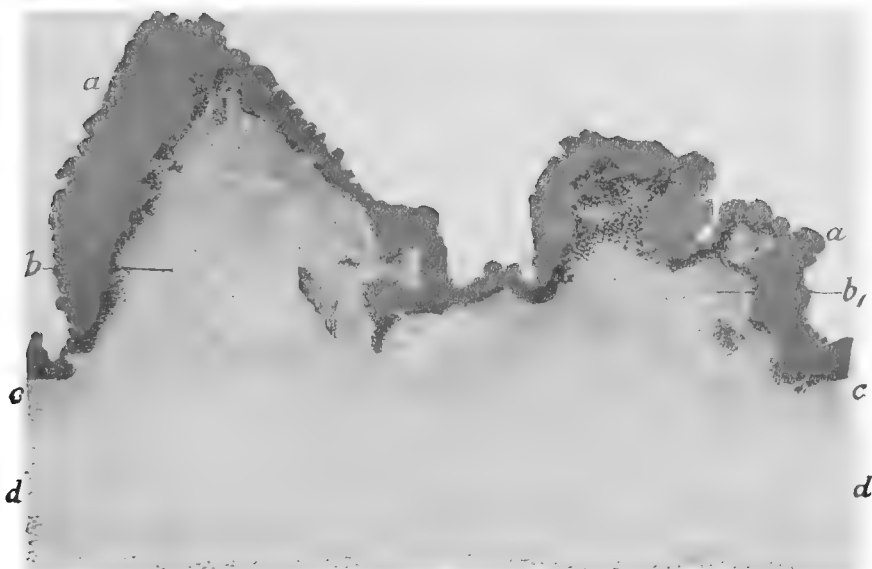
FIG. 395.—Endocarditis of the wall of the left auricle, due to streptococci (alcohol, methyl-violet, carmine). *a,* Masses of cocci; *b, b₁,* leucocytes and coagula; *c,* area of proliferation; *d,* inflamed endocardium. × 100.

pneumoniæ may also cause other inflammatory processes bearing the character of a catarrhal or bronchopneumonia. During the course of the disease the cocci are found in the inflamed areas, in greatest numbers at the beginning of the inflammation; they lie free in the alveoli (*b*) and clinging to cells (*d*). They are also found in parts of the lung bordering on the inflamed area, in the pleura, and under certain conditions in the pericardium, peritoneum, meninges, accessory nasal cavities, cellular tissue of the neck, in the mediastinum, submucosa of the soft palate and pharynx, in the conjunctiva, and skin. In all these places they may give rise to inflammatory changes. At times they may be demonstrated in the spleen, and in the blood, and in pregnant women may pass into the fœtus (Viti). Under certain circumstances they may be *widely distributed through the body;* and may cause, in the meninges, pleuræ, pericardium, and peritoneum, fibrinous, serofibrinous, and at times seropurulent and fibrinopurulent inflammations, without giving rise to pneumonia. Further, they may cause inflammations of the conjunctiva, middle ear, endocardium, joints; these inflammations may lead to suppuration. In many cases the mouth and nasopharynx appear to be the avenue of entrance — in these regions the cocci are not infrequently found in healthy in-

dividuals. Correspondingly, in cerebral and cerebrospinal meningitis the maxillary cavities, tympanic cavity, and the ethmoid labyrinth often contain exudates with diplococci. They are found in the exudates in all the forms above mentioned; the gelatinous capsule may present a variable thickness.

When inoculated into rabbits, guinea-pigs, and mice, the **Diplococcus pneumoniæ** increases in the form of encapsulated cocci, particularly in the blood and serous cavities, and may cause pneumonia with bloody serous exudate. When injected beneath the skin of the rabbit's ear (*Neufeld*) they produce erysipelatous inflammations. Rabbits are especially susceptible; they die with symptoms of septicæmia in from thirty-six to forty-eight hours after subcutaneous inoculation.
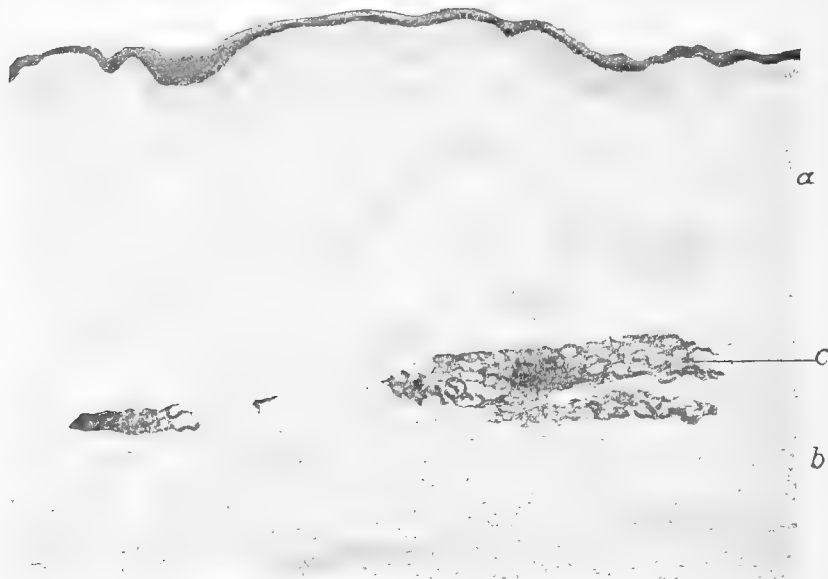
Fig. 396.—Erythema multiforme, due to streptococcus infection, arising in the middle ear (Fig. 393), from a child eight months old. Section through a red spot in the skin of the back of the foot (alcohol, methyl-violet, carmine). *a*, Corium; *b*, subcutaneous tissue; *c*, capillaries filled with streptococci. × 46.

The injection of pure cultures into the pleural cavity of rabbits gives rise to pleuritis as well as splenization of the lung, in which the parenchyma of the organ is filled with a hæmorrhagic serous exudate.

According to *A. Fränkel* the cocci easily lose their virulence, particularly when cultivated on milk; and if it is desired to retain their virulence they must, from time to time, be passed through susceptible animals. Cultivation of the cocci at 42° C. for one or two days destroys their virulence.

It may be regarded as demonstrated that the *Diplococcus pneumoniæ can cause meningitis;* there also exists a coccus, the **Diplococcus intracellularis meningitidis** (*Weichselbaum*), which is different from the pneumococcus and is to be regarded as the *cause of epidemic cerebrospinal meningitis. Albrecht, Ghon,* and *Weichselbaum* point out its great similarity to the gonococcus. It is found in the nasal secretions of epidemic meningitis and also in that of individuals coming in contact with such cases. In the cerebrospinal exudate it is found particularly in the polynuclear leucocytes. The essential pathological lesions are inflammatory changes in the membranes of the cord and brain, and in the tissue of the brain, cord, and nerves. *Flexner* and *Jobling* (*Jour. Amer. Med. Assoc.,* July, 1908) report encouraging results in the treatment of epidemic meningitis with a serum prepared in the horse by inoculation of *Diplococcus intracellularis.*

Pneumotoxin is formed by pneumococci most abundantly in the human and animal organism, but only sparsely in nutritive media (*Isaeff*). It is doubtful whether bactericidal antibodies or antitoxins arise during the course of the disease. It is therefore probable that the pneumotoxin does not belong to the true toxins. *Animals may be immunized* in various ways against pneumococci, and the serum of an immunized animal may be used as a healing serum. The results of treatment in man are still doubtful. Difficulties arise through the fact that pneumonia can be caused by other bacteria (pneumo-bacilli, pus cocci, influenza-bacilli, etc.).

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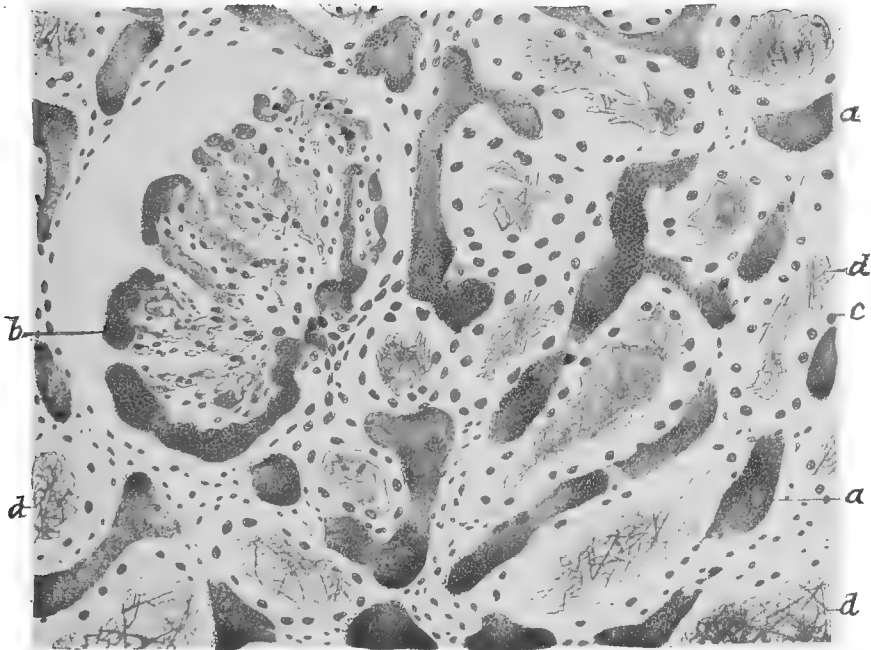
Fig. 397.—Extreme streptococcus infection of the kidney (grayish areas), arising after streptococcus angina (alcohol, Weigert's stain). *a*, Cocci in the intertubular; *b*, in the glomerular capillaries; *c*, urinary tubules; *d*, fibrin in the urinary tubules. × 280.

Meningitis cerebrospinalis. Fortschr. d. Med., v., 1887; Aetiologie u. path. Anatomie der Endocarditis. Beitr. v. Ziegler, iv., 1888: Seltenere Localisation des pneumonischen Virus. Wien. klin. Woch., 1888; Der Diplococcus pneumoniæ als Ursache der primären acuten Peritonitis. Cbl. f. Bakt., v. 1889; Diplococcus pneum. u. Meningokokken. Handb. d. path. Mikroorg., iii., 1903.

§ 154. The **Staphylococcus pyogenes aureus** or **Micrococcus pyogenes** consists of spherical cells occurring singly or in pairs, by multiplication forming grape-like clusters. The cocci are easily stained by various aniline dyes, and by Gram's method. They are facultative anaërobes, but grow better when supplied with oxygen.

The staphylococcus thrives on all culture-media, even at room-temperatures, though better at 37° C. It forms colonies which produce pigment in those parts exposed to the air and become orange-yellow. The pigment-formation is most marked on agar and potatoes. Gelatin is slowly liquefied. In the presence of grape-sugar it forms lactic, acetic, and valerianic acid. In bouillon-cultures there are produced poisons of violent action. The Staphylococcus pyogenes is one of the most frequently occurring pathogenic bacteria, and is, with Streptococcus pyogenes, the most common cause of **suppuration**. Both forms are therefore designated **pus-cocci**. It is widely distributed through the external world, and has been demonstrated in milk, wash-water, and waste-water,
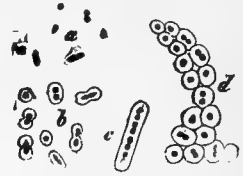
Fig. 398.— Diplococcus pneumoniæ. (Weichselbaum.) *a*, Cocci without capsule; *b*, single and double cocci with a gelatinous capsule; *c*, chain of encapsulated cocci; *d*, colony of cocci. × 500.

Fig. 399.—Diplococcus pneumonia in early stage (formalin, fuchsin). *a*, Hyperæmic vessels; *b*, diplococci; *c*, cellular exudate; *d*, swollen epithelial cells covered with cocci. × 500.

as well as in the air of operating-rooms and sick-chambers. Increasing in the tissues of the human body (Figs. 400-402) it causes *tissue-degenerations* and *necroses* followed by *inflammation* (Figs. 400, *d, e;* 401, *b, c;* 402, *c, d*) which is usually *purulent in character*, but not infrequently it *does not lead to suppuration.*

The *suppurations* produced by staphylococci are usually *circumscribed* (Figs. 400, 401), and show less tendency to involve surrounding tissue than the suppurations caused by streptococci. In the skin they give rise to *furuncle,* and *cutaneous* and *subcutaneous abscesses.* In the osseous system they are the most frequent cause of suppurative *osteomyelitis* Fig. 402) and *periostitis.* They not infrequently cause *purulent inflammations of the liver, lungs, pleura, peritoneum, brain, meninges, muscle, myocardium, spleen, kidneys, joints,* etc.; and are often the cause of *inflammations of the endocardium.* Since the virulence of staphylococci varies, they may produce, in the regions named, *transitory inflammations which heal with or without scar-formation.*

The *portal of entrance* of staphylococci is often easily recognizable (especially wounds), and the same is true of the path of *metastasis* to internal organs, whereby *inflammations of the lymph-vessels (lymphango-*
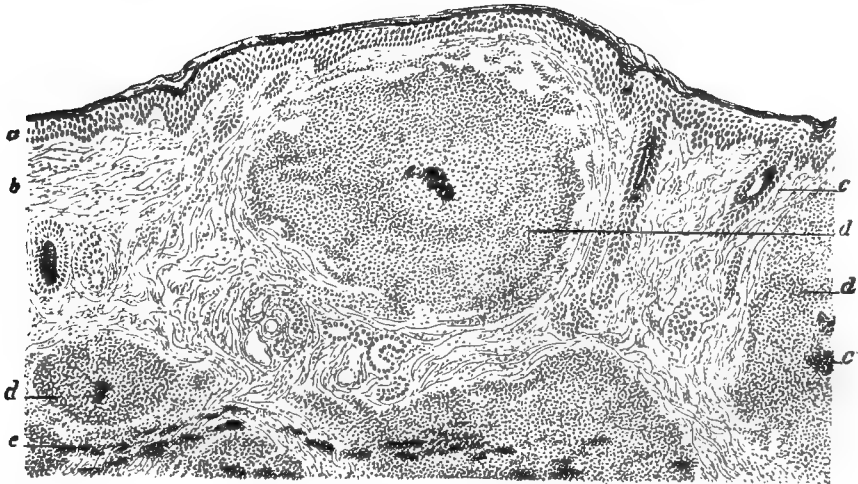
FIG. 400.—Multiple abscesses of the skin due to staphylococci (alcohol, carmine, Gran.'s method). Child of three weeks. *a,* Epithelium; *b,* corium; *c,* hair-follicle; *d, e,* purulent foci with cocci. × 40.

itis) and *of the blood-vessels (phlebitis, arteritis)* make their appearance. **Cryptogenic infections** are, however, not infrequent, so that the first recognizable localization of the infection appears in the endocardium, myocardium, or bone-marrow. The spread of staphylococci through the blood leads to multiple localizations with abscess formation; this condition is designated **pyæmia.** The complication of staphylococcus infection with severe symptoms of intoxication is known as **septicæmia;** and the combination of staphylococcus-pyæmia with septicæmia is known as **septicopyæmia** (cf. § 11).

Staphylococcus pyogenes aureus is also pathogenic for animals: horse, dog, cattle, goat, sheep, rabbit, guinea-pig, and mouse, particularly for the first-named, less so for the last. In these animals, it causes suppuration. The staphylococcus loses its virulence easily in cultures. The inoculation of cultures of high virulence into susceptible animals causes gelatinous œdema.

Related to the Staphylococcus pyogenes aureus are the **Staphylococcus pyogenes albus** and the **Staphylococcus pyogenes citreus.** The *albus* forms whitish, the *citreus* lemon-yellow colonies. The former is the cause of the so-called " stitch-abscesses " in surgical wounds, but is otherwise of negligible significance.

Staphylococcus pyogenes aureus usually occurs alone in pus-foci, but may be associated with other pus-cocci or even bacilli, for example, the Bacterium coli commune, or the typhoid-bacillus.

The **staphylococcus** forms a hæmolysin and a leukocidin (*Van der Velde, Neisser*, and *Wechsberg*) which destroys the leucocytes of rabbits, and also poisons which have a degenerative action on the tissues. The bodies of dead staphylococci cause inflammation when injected into tissues. Staphylolysin and hæmolysin and leukocidin form in the organism *antistaphylolysin* and *antileukocidin* and therefore belong to the toxins.

A serum produced by pathogenic staphylococci will agglutinate both the homologous strain as well as the majority of other pathogenic strains (*Kloppstock* and *Bockenheimer*).
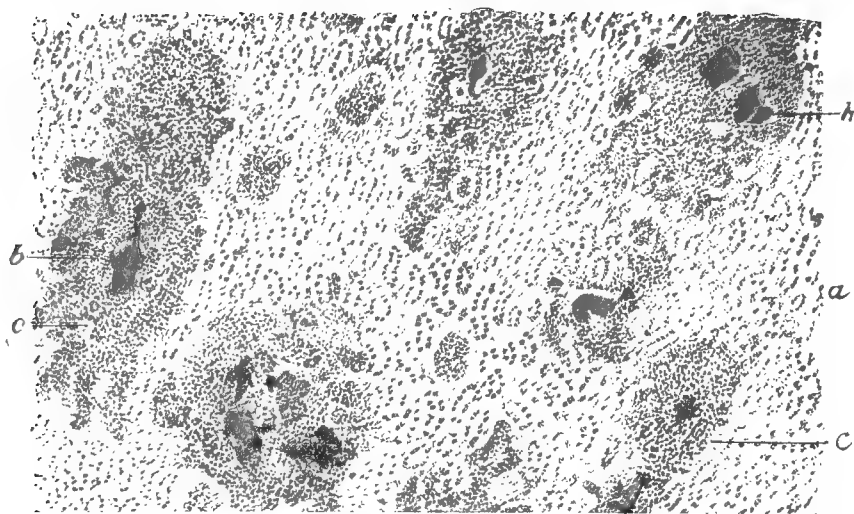
FIG. 401.—Miliary purulent nephritis, caused by staphylococci, primary focus in skin (furunculosis) (alcohol, methyl-violet, carmine). *a*, Normal kidney tissue; *b*, collections of cocci; *c*, purulent focus. × 43.

§ 155. The **Micrococcus Gonorrhœæ** or **Gonococcus** (Fig. 403) was described by Neisser in 1879. It is constantly present in the discharges of the purulent catarrh, known as gonorrhœa, of the male and female urethra, and the female genital canal (especially of the cervix), as well as in the secretions of gonorrhœal ophthalmia. It is universally regarded as the cause of gonorrhœa. Besides the specific cocci, other cocci may be present in gonorrhœal secretions, some of them closely resembling the gonococcus; pus-cocci may also be present.

The gonococcus may be cultivated on coagulated human blood-serum, blood-serum gelatin, on human blood-serum-agar, on urine-agar; and forms on the surface of the nutrient medium a thin grayish-yellow layer having a smooth surface. It dies easily, and grows only at higher temperatures.

The gonococcus contains a poison (Wassermann) which, when injected into the tissues, excites inflammation.

Animals are immune against inoculations with the gonococcus with the exception of the higher apes. Efforts to inoculate human beings with artificially cultivated gonococci have been successful in producing purulent catarrh of the inoculated mucous membrane.

In the purulent secretion of the mucous membrane infected with gonorrhœa the coccus usually forms clumps, and appears in the form of diplococci, the opposing surfaces of which are flattened (Fig. 403); but occurs also free (a), and inclosed within cells (b). It stains easily with aniline dyes, but is decolorized by Gram's method.

The gonococcus penetrates into the epithelial layer of the affected
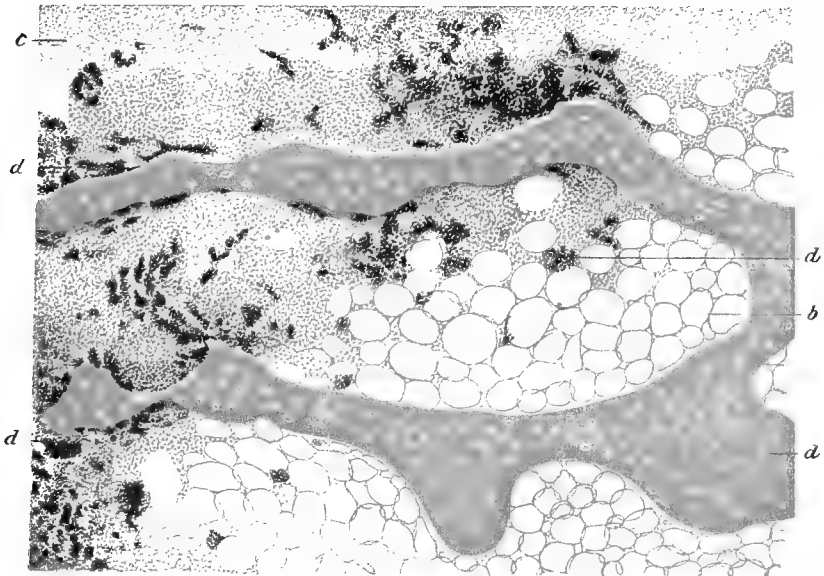
FIG. 402.—Staphylococcus osteomyelitis of calcaneus. (Alcohol, methyl violet, carmine.) a, Trabeculæ of bone; b, fatty marrow; c, purulent area; d, cocci. × 100.

mucous membrane, and lies between and in the epithelial cells, and in leucocytes. Only the uppermost layers of the connective tissue are infiltrated. The infiltration is most marked in the case of cylindrical epithelium, while in regions covered by squamous epithelium (fossa navicularis, vagina) the cocci lie more superficially. They cause inflammations which bear the character of *purulent catarrhs,* and are associated with cellular infiltration of the tissue of the mucosa (Fig. 404, *b, c, d*) and with epithelial desquamation. The male and female urethra and the adjoining parts of the genital glands and ducts and the urinary passages form the chief seats of localization. According to Scholz there occurs, after three-weeks' duration of the disease in the male urethra, metaplasia of cylindrical into stratified squamous cells, and the secretion decreases after this time. To what extent the deeper inflammations so

frequently accompanying or following gonorrhœa (peri-urethral abscesses, prostatitis, epididymitis, vesiculitis, cystitis, inflammation of the ducts of Bartholin's glands, salpingitis, ovaritis, pelvic peritonitis, arthritis, etc.) are to be referred to the spread of the gonococcus or to what extent to secondary infections by pus-cocci is a question. There can be no doubt that the gonococcus may become widely spread over the surface of mucous membranes. It has been demonstrated in the blood, in the inflamed epididymis, tubes, ovaries, joints, cardiac valves, tendon-sheaths, bursæ, in peri- and parametritic foci of inflammation, and in peri-urethral abscesses. In these cases it is usually regarded as the cause of the inflammation, yet the processes which lead to suppuration, and even the metastases in distant organs, appear to be more frequently dependent on the presence of pus-cocci.

FIG. 403.—Gonococci in the urethral secretion from a fresh case of gonorrhœa (methylene-blue, eosin). a, Mucus with single cocci and diplococci; b, pus-cells with, c, pus-cells without diplococci. × 700.

Gonorrhœal infection is at the beginning an acute process, but may become chronic, and is cured with great difficulty, since gonococci maintain themselves in the urethra, tubes, etc., for years, and continue to cause inflammation.

Irons (Jour. Infect. Dis., 1908) found that the injection of dead gonococci into individuals suffering from chronic gonococcus infections gave a "gonococcus-reaction" which may be of assistance in diagnosis.
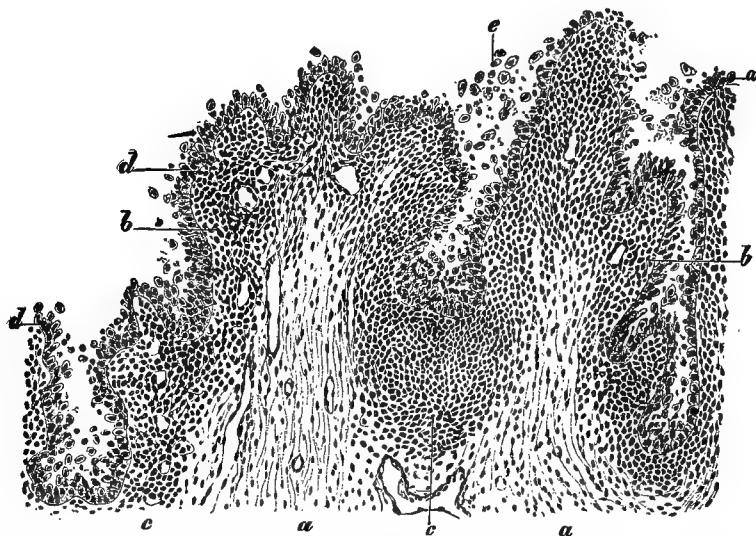
FIG. 404.—Urethritis gonorrhoica. Cross-section through the mucous membrane which had been thrown into folds (Müller's fluid, hæmatoxylin, eosin). a, Normal connective tissue; b, c, inflammatory, infiltrated, proliferating connective tissue of the mucosa; d, infiltrated and desquamating epithelium; e, desquamated epithelial cells and pus-corpuscles. × 100.

2. The Bacilli and the Polymorphous Bacteria, and the Pathological Processes Produced by Them.

(a) General Considerations Regarding Bacilli and the Polymorphous Bacteria.

§ 157. Under the designation **bacilli** may be classed all those bacteria which occur in the form of straight rods or rods which are slightly bent in one plane.

The **bacilli** multiply by division. The rods grow in length, and divide into approximately equal parts through the formation of a transverse partition-wall. If the division of one of the elongating bacilli is delayed, or if the separation of the individual rods from one another is not distinctly recognizable, there arise long, unbranched rods or threads (Fig. 406, *b*). If the divided rods remain attached to each other, there
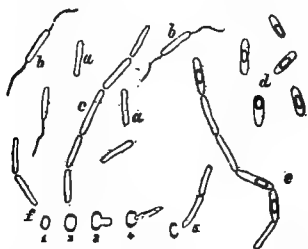
FIG. 405.   FIG. 406.

FIG. 405.—Bacillus subtilis in various stages of development (Prazmowski). *a*, Single rods; *b*, rods with flagella; *c*, chain of rods; *d*, single cells with spores; *e*, chain of rods with spores; *f* 1—5, germination of a spore. × 800.
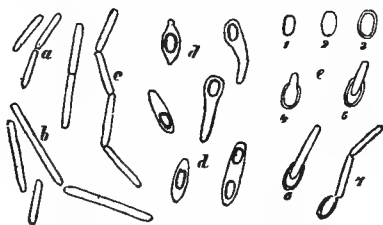
FIG. 406.—Clostridium butyricum (Prazmowski). *a*, Short rods; *b*, long rods; *c*, chain of rods; *d*, cells with spores; *e* 1—7, germination of a spore. × 800.

are formed chains of rods (Figs. 405, *c;* 406, *c*). In many forms of bacilli the ends of the individual rods are blunt, in others rounded or pointed.

In many bacilli, resting as well as swarming stages are observed. Flagella serve as the organs of motion (Fig. 405, *b*); they are situated sometimes at the ends, sometimes on the sides, of the rods, and may occur in large numbers. In many bacilli endogenous **spore-formation** is observed (Figs. 405, *d, e;* 406, *d*), the spores lying sometimes in the middle, sometimes at one end, of the cell. Not infrequently the spores appear within jointed threads. The germination of spores results in the formation of new rods (Figs. 405, *f*, 1-5; 406, *e*, 1-7).

During spore-formation the rods usually do not change their shape to any marked extent. In other cases they assume a spindle-, club-, or pear-shape (Fig. 406, *d*).

The **polymorphous bacteria** are distinguished from bacilli by the fact that they form, besides rods, long threads, with false or true branching; in individual cases a basal non-proliferating end and an apical proliferating end may be distinguished. In this category may be placed the fungi designated *Streptothrix, Cladothrix, Beggiatoa,* and *Crenothrix.* They are placed with the bacilli, because their botanical position is not

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definitely determined, while, in so far as they are pathogenic, they conform closely to the bacilli in their biological properties (*cf.* diphtheria-bacilli, tubercle-bacilli and actinomyces).

The **saprophytic bacilli** produce various forms of *fermentation* by their growth in nutrient fluids; many form *pigments.* A sharp line cannot be drawn between saprophytic bacilli and pathogenic forms, since some saphrophytes (*proteus vulgaris, Bacillus pyocyaneus, B. tetani, B. œdematis maligni*) occasionally develop in the human organism. Some also form *toxins* (*B. botulinus, B. pyocyaneus*) which when taken into the organism produce intoxication.

Bacillus botulinus (Van Ermengem) is an obligate anaërobic bacillus which develops occasionally in sausage, particularly in blood and liver sausages, in smoked meat, canned meats, game pies, salted fish, and in preserved fruits and vegetables. The bacillus is 4–6 μ long, 0.9–1.2 μ broad and possesses 4–8 peripherally arranged flagella. It stains according to Gram. In ordinary nutritive media it grows best under anaërobic conditions at a temperature of 18°–25° C., and forms endogenous spores. Acids inhibit its growth.

When growing in the foods mentioned, it produces a toxin which is poisonous for experimental animals, and causes the formation of an antitoxin. The poison is rendered inactive by heating to 80° C., but is not changed by the digestive juices. The consumption of food in which the bacillus has already formed its toxins leads, therefore, to intoxication. On the other hand, the bacillus does not develop in the human organism, its growth being hindered by the high body temperature. The bacillus should be classed as a *toxicogenic saprophyte.*

The intoxication known as botulismus comes on about twenty-four to thirty-six hours after the taking of poisoned food, and is characterized by nervous disturbances of central origin (paralysis of accommodation, mydriasis, ptosis, and double vision), dryness and redness of the mucous membrane of mouth and pharynx, aphonia, dysphagia, etc. Constipation and retention of urine frequently take place, or there may be diarrhœa and vomiting. Death often results after a short time through bulbar paralysis.

It has been shown that the designation botulism, or sausage poisoning, is inappropriate to this form of bacterial intoxication, at least as it occurs in the United States. Canned string beans, asparagus, corn, apricots, ripe olives and cheese have at various times and places been implicated. The majority of outbreaks recorded in this country have been due to household canned foods, but the bacillus may also find its way into canning factories. In either event, the spores of the causative micro-organism may survive relatively high temperatures and subsequently germinate to produce a potent toxin, the ingestion of which gives rise to symptoms of poisoning. There seems to be no doubt that the early statements of Van Ermengem relative to the low heat resistance of this organism are incorrect as applied to all strains. For example, most of the American strains have been found to withstand much higher temperatures, some even resisting the temperature of boiling water for a considerable period. Outbreaks of botulism have been recorded in Belgium, France and Germany. Thus far, Great Britain appears to have been exempt. In the United States, the majority of cases have been reported from California, Idaho, Colorado, Indiana, Massachusetts, Michigan, New York, Kentucky and Illinois, so that the disease occurs in widely separated parts of the

country.   Several recent outbreaks have been traced to canned ripe olives. (Journal of the American Medical Association, December 13 and 20, 1919.)

As **Proteus vulgaris,** Hauser has described a bacillus which is frequently present in decomposing animal substances and in human cadavers, and in gangrenous ulcers.   It forms rods of varying length, and produces substances poisonous for animals.   It is not infrequently found in *human tissues,* in association with streptococci, pneumococci, and diphtheria-bacilli; and by its presence aggravates infection and causes *putrid decomposition* of pus and necrotic tissue.   In rare cases it may *alone cause inflammation,* particularly of the urinary bladder (*cystitis*).   Cases of *hæmorrhagic enteritis* have been described, in which a form of proteus was regarded as the causal agent.

The **pathogenic bacilli** and **polymorphous bacteria** cause both acute and chronic affections, the former terminating in death or in healing after destruction of the bacteria.   In acute diseases the bacteria may remain in the body for a long time after the disappearance of symptoms. The chronic affections are characterized by persistence and multiplication of the bacteria in the body, so that the disease assumes a progressive character, and sometimes slowly, sometimes rapidly, new regions are invaded and suffer changes.

Bacillus subtilis is a fission-fungus whose spores are widely distributed in the ground, in hay (hay-bacillus), and in the air.   When cultivated on potato or on the dung of herbivorous animals, it forms whitish-yellow colonies; on liquids it forms pellicles.   It requires oxygen for development.

The fully developed rods (Fig. 405, *a*) are 6 μ long.   The snake-like motions occurring at times are produced by lateral and terminal flagella.   Through the growth of the rods undivided threads are formed which after division form chains of rods.   The separate cells may develop in their interior glistening, sharply contoured spores (*d, e*), which lie either in the middle or nearer to one end of the cell.   Later the cells in which the spores have been formed die.   During germination the spores become pale (Fig. 405, *f*, [1-5]), lose their glistening appearance and sharp contour.   A shadow then appears at each pole, while the spore begins a tremulous motion.   After a time the contents of the spore project from the membrane of the spore in the form of a germinal utricle, which later becomes elongated, divides and produces swarming rods.

Bacillus prodigiosus grows on potatoes and bread, as well as on agar-agar, and on gelatin, liquefying the latter.   It forms a red coloring matter which is soluble in alcohol.   The pigment is formed only in the presence of oxygen; in the growth in milk the coloring-matter is contained in the fat-droplets.   The bacilli themselves are colorless.

Bacillus pyocyaneus occurs occasionally in bandages on suppurating wounds and causes a greenish-blue discoloration of the same.   The coloring-matter called *pyocyanin* is soluble in chloroform and crystallizes from the solution in long blue needles.   In addition, it forms a coloring matter soluble in water that produces a greenish fluorescence of gelatin.

(b) The Pathogenic Bacilli and Polymorphous Bacteria.

§ 158.   The **Bacillus anthracis** (*Bacteridie du charbon*) is the *cause of anthrax,* a disease occurring chiefly in cattle and sheep, occasionally transmitted to man.   It is a fission-fungus which, when inoculated into a susceptible animal, increases locally in the tissues and later enters the blood.

Anthrax-bacilli (Fig. 407) are 3 to 10 μ long and 1 to 1.5 μ broad. In the blood of animals affected with anthrax they occur either singly or in thread-like jointed bands of two to ten rods, whose ends are sharply

cut across (Figs. 407, 408), more rarely concave or slightly convex. They possess a gelatinous capsule which is best brought out by staining dried preparations by the method of His or Welch. They can be cultivated on blood-serum-gelatin, in bouillon, on slices of potatoes or turnips, and on plain agar, in the presence of oxygen, and grow most rapidly at a temperature of from 30° to 40° C. At temperatures below 15° and above 43° C. development is impossible.

Under suitable conditions of growth the rods increase in length, and within a few hours form non-encapsulated threads of considerable length. These consist of short segments whose outlines may be made visible by treatment with iodine or by stains (Fig. 408). Ten hours later the clear contents of the threads become granular, and at regular intervals there become a p p a r e n t bodies which, after a few hours,

FIG. 407.—Section from a liver whose capillaries contain numerous anthrax-bacilli and scattered leucocytes (alcohol, gentian-violet, vesuvin). × 300.
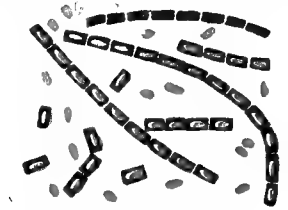
FIG. 408.—Spore-containing anthrax-bacilli and free spores. Cover-glass preparation from a culture of the bacilli grown in the incubator upon a potato, and stained with fuchsin and methylene-blue. × 800.

enlarge into strongly refractive spores (Fig. 408). Later the threads disintegrate and the spores become free.

If the bacilli or spores gain entrance to the blood, they increase and form rods as described, that stain with aniline dyes, and by Gram's method. Sections of hardened tissue show that they are present in large numbers in the capillaries (Fig. 407), particularly in the spleen, liver, lungs, and kidneys. The neighboring parenchyma appears unchanged; still local proliferation of the bacilli can cause tissue-degeneration, necrosis, and hæmorrhagic inflammation. If infection of the blood takes place during pregnancy the infection may pass to the fœtus.

Anthrax-bacilli or their spores may gain entrance into the skin of man through small wounds, an event which is particularly likely to happen in individuals who butcher, or shear, or prepare the skins of animals infected with anthrax; occasionally infection may be transmitted by means of the sting of a fly which has taken up blood from an animal infected with anthrax. Infection not uncommonly is due to the use of shaving brushes made of infested hairs or to the wearing of contaminated furs. There develops at the place of infection a pustule (Fig. 409) from 6 mm. to several centimetres in diameter, having an arched or flattened surface, and a red or yellowish color. This is after a time covered with vesicles, or after the loss of epithelium becomes moist, so that through drying of the exudate, a scab is formed (Fig. 409, g).

The centre may become depressed through the formation of an area of softening, so that the edges form a wall about the latter. The neighborhood of the pustule is sometimes but slightly changed, at other times reddened and swollen, and may be set with minute yellow or bluish-red vesicles. If the process remains local, the gangrenous pustule may be thrown off. Infection of the blood is fatal. In rare cases the infection from the beginning may show itself as an extensive, intense, œdematous swelling of the tissue without the formation of a circumscribed elevation (malignant anthrax œdema).

In the region of a fully developed anthrax-pustule (Fig. 409), the corium (d, d_1) and the papillary body (c) are infiltrated with serocellular exudate as well as by bacilli. The bacilli lie particularly in the outer portions of the corium (d_1) and in the papillary body (c), but may pene-

FIG. 409.—Section from an anthrax-pustule ten days old, taken from the arm of a man (alcohol, Gram's method, vesuvin). a, Epidermis; b, corium; c, papillary body œdematously swollen and infiltrated with exudate and bacilli; d, outer layer of corium, infiltrated with cells; d_1, the same containing also bacilli; e, deep layers of the corium infiltrated by cords of cells; f, dermal tissue infiltrated with bacilli and cells; g, bloody exudate containing bacilli, lying upon the surface; h, hair-follicle; i, sweat-gland. × 33.

trate the deeper layers of the corium (f). In the neighborhood of the papillary body (c) the exudate is sanguineous. Vesicles filled with bloody fluid result, if the exudate extends to the epithelial covering, and if the deeper portions of the latter become liquefied, permitting lifting of the superficial layers by the exuded fluid. If the upper layers of the skin are lost, the bloody fluid containing bacilli (g) appears on the surface.

The cellular infiltration has its seat chiefly in the corium (d, d_1, e), and the impression is gained that massing of cells forms a protection against the spread of the bacilli. The cells which collect belong for the greater part to the polynuclear leucocytes (Fig. 410). The bacilli lie sometimes in, sometimes between the cells.

If infection with anthrax-spores takes place in the intestinal canal, an event which occurs most frequently in the small intestine, less often in the stomach and large intestine, there develop dark-red or brownish-red hæmorrhagic foci, the size of a lentil or bean or larger, with a grayish-yellow or greenish-yellow slough in the centre. In other cases the crests of the folds of the mucosa are swollen and hæmorrhagic, and show evidences of sloughing. The mucosa and submucosa are infiltrated with blood in the region of the foci; the surrounding tissues are œdematous and hyperæmic. Bacilli are found in the tissues in and about the foci, particularly in the blood- and lymph-vessels, and may be demonstrated in neighboring lymph-nodes.

Primary lung infection may occur in man as the result of inhalation of anthrax-spores, proving fatal in from two to seven days. Individuals who handle the hair of animals that have died of anthrax are especially exposed to infection; the *rag-sorter's disease,* which occurs in men and women employed in the sorting of rags in paper-factories, is an anthrax infection. The spores taken into the lungs in respired air develop in the bronchi and alveoli, in the lymph-spaces of the lungs and pleura and in the bronchial nodes, and penetrate into vessels. Their growth causes inflammatory hæmorrhagic processes in the lungs, as well as hæmorrhagic exudations into the pleural cavity and mediastinal tissue, and swellings of the lymph-nodes. It may also lead to necrotic foci in the lungs and in the bronchial and tracheal mucosa.

Fig. 410. — Portion of anthrax pustule from the arm (Fig. 409), containing bacilli. × 350.

Mice, rabbits, sheep, horses, and sparrows are susceptible to anthrax; white rats, dogs, and Algerian sheep are less susceptible or immune. Cattle are easily infected through taking in of spores from the alimentary canal, but are less susceptible to inoculation. Formation of spores does not take place in the tissues and blood.

Among certain animals, geographically as well as zoologically, anthrax is the most widespread of all acute infective diseases. In occasional instances it is transmitted to man, usually through abrasions of the skin that have been in contact with infested hides, furs, shaving brushes made of contaminated hairs, and the like, but sometimes by swallowing or breathing. In recent years the occurrence of anthrax in human beings has undergone increase and is now regarded by students of industrial conditions as an occupational disease of moment. Moreover, in view of the fact that hides, furs and other products of anthrax-infested districts are seldom, if ever, subjected to disinfection before shipping, it is to be expected that anthrax will undergo still further increase as our trade with the cattle countries enlarges. In this climate anthrax is most often encountered among handlers of hides imported from the Argentine and Far East. Sometimes the disease appears in epidemic form among longshoremen engaged in unloading the same cargo.

Malignant anthrax oedema of the face and neck is practically always fatal. In the same way the so-called wool-sorters' disease, which is an anthrax septicemia with intense pulmonary and cerebral symptoms, and anthrax of the intestinal tract, are likewise deadly. The malignant pustule, on the other hand, not infrequently heals and the patient recovers. In malignant pustule of the face, however, the mortality is five times greater than that of an extremity, in which only a small percentage of cases terminates fatally. In the past four years 20 cases of malignant pustule have been treated at Bellevue Hospital. Of these, 13 recovered. This variety of anthrax is, at the beginning, a purely local lesion. The malignant pustule is a characteristic and easily recognized lesion. At the site of inoculation a small papule appears and within a few hours is surrounded by extensive œdema. **The**

papule rapidly undergoes enlargement and central necrosis attended by the forma-
tion of a series of silvery vesicles scattered over the scab or immediately circum-
ferential to the necrotic zone. The patient's mentality is usually preserved through-
out. The swelling of the tissues in the immediate vicinity of the pustule may be
extreme and depends on infiltration by so-called anthraco-mucin, which is a pro-
tective substance. In it anthrax bacilli do not thrive. Incision of the œdematous
area, therefore, is contraindicated.

In recent years the serum treatment of anthrax has received a great deal of
attention. The serum is injected intravenously in large doses at frequent inter-
vals. Local injection of serum at multiple points in the immediate vicinity of the
anthrax pustule is an exceedingly important part of the specific treatment and should

FIG. 411.—(Bellevue Hospital.) Anthrax pustule of left side of neck showing the wide-
spread swelling of the surrounding tissues due to infiltration by anthraco-mucin.

never be neglected. There are those who advocate at the same time excision or
cauterization of the pustule, while others depend entirely on the local injection of
serum to control the infection. After the bacillus invades the blood stream, of
course, the outlook is hopeless, serum or no serum.

The bacilli of anthrax are killed by high temperatures, drying, and through
decomposition of the nutrient fluid. The spores, on the other hand, are resistant,
and are usually the medium of spread of the disease.

The colonies on gelatin show a wavy, irregularly shaped margin, and consist of
interlacing strands or threads, which grow out of the culture in all directions.
The gelatin is liquefied immediately about the culture. On potato the bacillus forms
grayish-white, slightly granular colonies having a sharply outlined border. On
blood-serum it forms a white coating.

Stab-cultures in gelatin are white and during the process of growth radiate at
right angles from the line of inoculation into the gelatin, particularly near the sur-
face. After liquefaction of the gelatin they sink to the bottom.

Marked attenuation of anthrax-bacilli may be produced by keeping the bacilli
for ten minutes at a temperature of 55° C. (*Toussaint*) or for fifteen minutes at

52° C., or for twenty minutes at 50° C. (*Chauveau*), or through the influence of oxygen under high pressure (*Chauveau*). The bacilli attenuated by exposure to high temperatures quickly regain their virulence; those attenuated at lower temperatures remain weakened for many generations.

The addition of carbolic acid to the nutrient fluid in a proportion of 1:600 permits the development of anthrax-bacilli, but destroys their virulence within twenty-nine days (*Chamberland, Roux*). Likewise, attenuation may be produced by the addition of potassium bichromate (1:2,000–1:5,000). The addition of carbolic acid up to 1:800 hinders the formation of spores.

Through cultivation of the bacilli at 42–43° C. (*Toussaint, Pasteur, Koch*) their virulence may be so weakened that they no longer kill first sheep, then rabbits and guinea-pigs, and finally mice. If the temperature is kept in the neighborhood of 43° C. this result may be obtained in six days; at 42° C. it may require about thirty days to decrease the virulence to this extent (*Koch*). By first inoculating with bacilli which kill mice but are harmless for guinea-pigs, and afterward with bacilli which kill guinea-pigs but not strong rabbits, immunity against anthrax may be obtained in sheep and cattle but not in mice, guinea-pigs, and rabbits. Such protective inoculations are, however, not of practical value, since, in order to protect against natural infection with spores from the intestinal canal, such virulent inocu-

FIG. 412.

FIG. 413.

FIG. 412.—Typhoid-bacilli from a pure culture. Streak-preparation (methylene-blue). × 1,000.
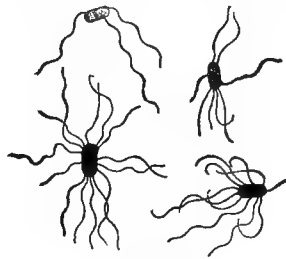
FIG. 413.—Typhoid-bacilli with flagella. (After Bunge.) × 1,200.

lation-material must be used that a large per cent. of sheep (ten to fifteen per cent.) die from the inoculations. Further, the protection afforded by the inoculation is of short duration, and the inoculation must be repeated within a year's time.

According to observations by *Roux* and *Chamberland* anthrax bacilli which are cultivated in bouillon to which a small amount of potassium bichromate (1:2,000) or carbolic acid (1 to 2:1,000) has been added, permanently lose their power of spore-formation while retaining their virulence.

True toxins or endotoxins have not yet been demonstrated in anthrax bacilli.

§ 159. The **Bacillus typhi abdominalis** (Fig. 412) is a fission fugus which occurs in the form of rods 2 to 3 μ long, having rounded ends, in cultures growing in pseudo-threads. It is regarded as the cause of *typhoid fever*, a disease which was once widely prevalent, but is now rarely encountered. In cultures the typhoid bacillus shows *lively movements* which are accomplished by flagella (Fig. 413) attached to the *sides* of the bacilli and to their *ends*. The flagella may be demonstrated by staining-methods.

The bacilli gain entrance to the body through drinking-water and food. They develop in the *solitary* and *agminated follicles of the small and large intestines,* as well as in the *mesenteric lymph-nodes,* and in the *spleen.* In the intestine they cause hyperplasia of the lymphoid tissues, which project above the surface as flattened or rounded elevations, and later undergo necrosis and sloughing with the formation of ulcers. In the

process of ulceration blood vessels may be opened with the production of haemorrhages of greater or less degree, or perforation of the gut may occur with the escape of intestinal contents into the cavity of the peritoneum and secondary peritonitis.

The *swelling of the lymph-nodes,* in the mesentery and vicinity, ends either in healing through absorption of the hyperplastic lymphoid cells, or may lead to necrosis. Rupture of necrotic lymph-nodes into the peritoneum sometimes occurs, and results in the escape of typhoid bacilli and peritonitis.

The *bacilli are usually distributed through other parts of the body,* and it is probable that inflammatory exudations in the lungs occurring during the course of typhoid fever are due to increase of the bacilli in the lungs. It should always be borne in mind that aspiration-pneumonias are of frequent occurrence in typhoid patients, and that *secondary infections* may take place from the intestinal ulcers and give rise to metastatic inflammations. The swellings of the mucosa and submucosa and of the perichondrial tissue, which occur in the palate, throat, and larynx, are in part the result of the specific infection, and in part of secondary disease. Typhoid-bacilli have been demonstrated in the blood, liver, gall-bladder, in the rose-spots of the skin, in the kidneys, central nervous system, testicles, in pleuritic and peritoneal fluids, in the periosteum, bone-marrow, etc. The bacilli circulate in the blood for about two or three weeks and cultivation from this source is often employed as a diagnostic method. When typhoid fever occurs during pregnancy the bacilli may pass to the fœtus.

In the course of typhoid fever there appear in the blood certain substances which cause degeneration of typhoid-bacilli (cf. § 31). This may be demonstrated by the fact that (Widal-Gruber reaction), through the addition of serum from an individual ill or convalescent from typhoid fever, to a bouillon-culture of freely motile typhoid-bacilli, the latter become motionless, clump (agglutination), and die. This reaction may be used as a means of diagnosis, but is not infallible, since agglutination may be produced by the serum of individuals who have not had typhoid fever, and may be absent in typhoid. The agglutinating power can last for years, or may vanish after a month.

Individuals who have had typhoid fever may harbor the bacilli in their bodies for years after the attack, without showing any symptoms of infection (*"typhoid carriers"*). By giving off bacilli through urine or fæces typhoid carriers become an element of danger to the community in which they live. ("Typhoid Bacilli Carriers." *Park, J. Amer. Med. Assoc.,* 1908.)

The **typhoid-bacillus** stains well in cover-glass preparations, with gentian-violet, alkaline methylene-blue, and Bismarck brown. It is decolorized by Gram's method. It is difficult to demonstrate it in sections of hardened tissues.

The bacillus may be cultivated on gelatin, agar-agar, and blood-serum, in milk, and on potato. On the last named it forms a coating which can be scarcely recognized by the naked eye; but when touched with a platinum wire it becomes apparent that it is covered with a pellicle.

On gelatin and agar-agar the bacilli form grayish-white, irregularly shaped, flat growths. *Gelatin is not liquefied.* Milk in which the bacilli are grown is not changed externally.

The cultures thrive at room as well as body temperature. Potato-cultures made in the usual manner, when kept between 30° and 42° C., produce rods which have glistening bodies in their poles. *Gaffky* regarded these as spores, and the majority of authors formerly accepted this view. According to *Buchner* and *Pfuhl,* however, these granules are degeneration phenomena, which occur particularly when acid is present in the culture medium. The polar granules represent condensed

protoplasm, and therefore stain in fresh preparations more quickly with aniline dyes than the other parts of the cell. The clear, colorless spots which are seen at the ends of the rods in dried and stained bacilli have been held to be identical with the polar granules and therefore regarded as spores, but are due, according to *Buchner,* to hollow spaces formed at the ends of the rods as the result of retraction of the protoplasmic tube following death and drying of the bacilli. Spore-formation has, therefore, not been demonstrated.

Cultures of typhoid-bacillus show few characteristic appearances and are with difficulty distinguished from those of other bacteria widely scattered in the outer world. Their properties are similar to those of *Bacillus coli communis* (§ 160). Certain points of difference are as follows: The typhoid-bacilli produce no indol, while similar bacteria, such as *Bacillus coli*, produce it, so that bouillon cultures become red through the addition of potassium nitrite and sulphuric acid. The typhoid-bacillus produces no gas in a two-per-cent. grape-sugar bouillon, while *Bacillus coli* produces gas. Finally typhoid-bacilli in milk cause weak acidity but no coagulation, while the *Bacillus coli* will cause at 37° C., even in twenty-four to forty-eight hours, strong acidity and coagulation of the milk. When typhoid bacilli are grown on agar colored blue with litmus, the color remains unchanged, while *Bacillus coli* decolorizes the blue.

In moist earth, in pure and impure water, typhoid-bacilli may remain alive for weeks. In artificial Seltzer water they do not die out for a longer period. In privy vaults and fæcal masses, or in earth saturated with fæcal matter they may live for weeks and months.

Inoculations of the bacilli in animals ordinarily used for experiment do not produce a disease corresponding to typhoid fever in man. Experimental investigations show, however, that the typhoid-bacilli produce active toxins (endotoxins?) which in large doses kill the animals, causing hyperæmia and swelling of the intestinal follicles, mesenteric nodes, and spleen. Cultures injected into the tissues cause local inflammation of greater or less intensity.

The value of the **agglutination test** is limited, since it is hard to decide whether the agglutinating effect of the serum is brought out by the same kind of bacillus or by a related variety. In general the serum of a patient agglutinates the species causing the disease in a greater dilution than in the case of a related organism, but there occur exceptions to this rule. According to *Lubowski* and *Steinberg* the agglutinatibility of typhoid-bacilli can be increased in guinea-pigs and rabbits through proteus or staphylococcus infection. Much more positive as a diagnostic method is the demonstration of typhoid-bacilli in the blood by means of cultures.

Paratyphoid fever is a disease similar to typhoid fever, but is caused by a form of bacillus of which a type A and a type B have been described. Clinically the disease runs a lighter course than typhoid fever and is rarely fatal. The anatomical findings are similar to those of typhoid fever, but the intestinal changes are less marked and ordinarily are confined to the colon. It is possible to make a differential diagnosis by means of the *Widal* reaction; yet it should be noted that paratyphoid serum may agglutinate typhoid-bacilli.

The **paratyphoid bacteria** stand, as far as their cultural characteristics are concerned, between the typhoid-bacillus and the Bacillus coli communis. The round, smooth-edged gelatin colonies of freshly cultivated strains do not show the superficial vein-like furrowing. In type A they are almost colorless, while in type B they are whitish. Both consist of short rods and are motile; they ferment sugar without coagulating milk; cause fluorescence in neutral-red media; grow as blue colonies on *Drigalski-Conradi* plates and do not produce indol in bouillon cultures. Type A forms more delicate pellicles than B, and grows on potatoes in a manner similar to the bacillus of typhoid fever. Milk is not changed by type A, while it is cleared (alkaline) after several weeks by type B.

§ 160. The **Bacillus coli communis** or *Bacterium coli commune* is a fission-fungus which is constantly present in the intestinal tract of man as well as of other mammalia. The bacilli are 2–3 μ long and 0.3–0.4 μ thick. They are motile and may possess as many as twenty flagella on one rod. The bacilli grow at room-temperature as well as at the temperature of the body. They form in gelatin small, round, white colonies; on its surface pellicle-like coatings. Upon potatoes they form moist coatings of the yellow color of maize or pease. They do not form spores; and are not stained by Gram's method.

Bacillus coli is similar to the typhoid bacillus, but may be differentiated by cultivation and by the employment of suitable reactions (cf. § 159). It was formerly regarded as a harmless saprophyte; but it cannot be doubted that it possesses pathogenic properties. Under suitable conditions (perforation or incarceration of the intestine, or impaction of fæces) it may pass into the peritoneal cavity and excite purulent inflammation, or at least take part with other bacteria in the production of inflammation. It not infrequently gains access to the bile-passages and gall-bladder, as well as to the descending urinary passages and the kidneys, giving rise to inflammations of varying intensity.

§ 161. Under the designation **Bacillus enteritidis** (Gärtner) there is a group of bacilli found in animals suffering from inflammations of the intestine, lungs, uterus, or udder, and with septicæmia. Gaining entrance into the human alimentary tract these bacilli excite more or less severe inflammations of the intestine characterized by swellings of the follicles. Man is infected by eating meat from animals slaughtered while in a diseased condition; such infection takes place most often through the meat of calves. Other sources of infection (drinking-water, milk, fish that have eaten diseased meat, oysters, etc.) are not excluded. The affection belongs to the group of meat-poisonings (see Bac. botulinus, § 157) occurring in the form of local epidemics.

The bacilli are short, often ovoid, at times motile, and possess four to twelve flagella. They are not stained by Gram's method. They form poisons that are resistant to high temperatures; and are pathogenic for mice, guinea-pigs, rabbits, calves, and apes. Injected into the tissue they cause local inflammation and give rise to hæmatogenous and lymphogenous metastases in different organs. Their entrance into the alimentary tract causes gastro-enteritis.

The **Bacillus enteritidis** was first studied by *Gärtner* in 1888 and recognized as the cause of the gastro-intestinal form of meat-poisoning. His findings were confirmed by the investigations of *Van Ermengem, Fischer, Durham, Thomassen, Petri,* and others. The bacillus is distinguished from other bacilli such as the *Bac. typhi, Bac. coli,* etc., by its cultural characteristics and by the agglutinating action of the serum of infected individuals or of previously immunized experimental animals. Surface colonies on gelatin are similar to those of the colon-bacillus. They form no indol, do not coagulate milk, but cause it to take on a yellow color; they ferment sugar with the production of gas. The infection is caused most often through the consumption of the flesh or organs of calves and cattle that have suffered from the various diseases designated as septicæmia of calves, dysentery, enteritis, pneumo-enteritis; and infectious inflammation of the intestine.

Intoxications caused by the consumption of meat undergoing ordinary putrid decomposition (*Proteus, Bac. coli*) are rare and are not severe. Game and cheese are often eaten in a condition of decomposition without exciting gastro-intestinal disturbances or other symptoms of intoxication.

§ 162. The **Bacillus dysenteriæ** is probably the cause of catarrhal, diphtheritic, hæmorrhagic, and purulent inflammations of the colon that are classed with epidemic *dysentery*. Besides this form of *bacillary* dysentery there occur affections classed as dysentery that clinically and anatomically are similar to it, but are due to other parasites, *amœbæ* in particular, or to chemically active substances (sublimate, septic poisons), or are induced by fæcal retention.

The dysentery bacillus is a plump, short rod, with rounded ends, often tapering. They have no flagella and are non-motile. They are easily stained by aniline dyes (methylene-blue, carbol fuchsin) and often show

polar staining. They are decolorized by Gram's method. On ordinary nutrient media the bacillus grows best at a temperature of 37° C., either under aërobic or anaërobic conditions.

According to American investigators, bacillary dysentery is due to a number of types of bacilli, differing in their fermentative action, bacteriolytic and agglutination tests. In the treatment of the disease *Shiga* recommends a polyvalent serum active against all types.

§ 163. The **Bacillus pyocyaneus** was first demonstrated in the pus of wounds in which it had produced a bluish-green discoloration. It is widely distributed throughout the outer world, being found particularly in liquid manure and dung-heaps, in water, and in the intestinal contents of animals (swine) and of man.

Bacillus pyocyaneus forms rods of varying size (0.6–1–6 μ). They possess a terminal flagellum. It is decolorized by Gram's method. Spores are not formed. It is easily cultivated on ordinary media and produces ferments that liquefy gelatin, coagulate milk, and break up albumin. It produces in the presence of oxygen, *bluish-green pyocyanin,* which is soluble in chloroform, and a *greenish fluorescent* pigment soluble in water but not in chloroform and which in gelatin cultures causes greenish fluorescence of the gelatin. For the majority of experimental animals it is pathogenic, particularly for guinea-pigs and goats, and causes inflammation at the seat of inoculation, but later may spread through the blood. In bouillon cultures it forms both a true toxin and an endotoxin.

FIG. 414.—Tetanus-bacilli with terminal spores. × 1,000.

§ 164. The **Bacillus tetani** is (Fig. 414) widely distributed through the superficial layers of the earth, and is the cause of tetanus. According to observations made by Nicolaier in 1885, it is possible to produce in mice, guinea-pigs, and rabbits, by subcutaneous inoculation of surface-earth, typical tetanus with fatal termination.

It was demonstrated by Rosenbach in 1886 that this bacillus is present at the seat of injury in tetanus in man following trauma or freezing; and that when inoculated into guinea-pigs and mice it again produces tetanus. This discovery has been corroborated.

The tetanus-bacillus is anaërobic and thrives in an atmosphere of hydrogen, but not in carbonic-acid gas. It grows on peptone-agar that is slightly alkaline, on blood-serum, and in nutrient gelatin. The latter is liquefied with evolution of gas. The addition of from 1.5 to 2 per cent. grape-sugar to agar accelerates the growth; a temperature of 36°–38° C. is most favorable for its development. The bacillus forms long, thin, bristle-shaped rods which develop spores (Fig. 414) giving rise to a spherical swelling at the end of the rod (knobbed bacilli). In cultures it may form long pseudothreads. Cultures give off an offensive odor; gelatin is slowly liquefied. The bacilli stain by Gram's method. They are motile except during the time of spore-formation, and possess peritrichous flagella. Pure cultures inoculated into horses, asses, guinea-pigs, mice, rats, and rabbits cause tetanus, but in rabbits larger amounts must be injected. The tetanic contractures begin in the neighborhood of the point of inoculation. Suppuration does not occur at the point of inoculation. The bacilli cannot be demonstrated after the death of the animal except at the seat of inoculation.

The specific action of the tetanus-bacillus is to be referred to a toxin (*tetanus toxin*) which, through its haptophore group, is bound to the cells of the nervous system, and after a certain period excites tetanic convulsions. An antitoxin is produced in the body of man and experimental animals and by it animals may be made immune against tetanus (see § 32).

The infection — intoxication — of man usually takes place through small wounds; idiopathic tetanus, which does not start from demonstrable wounds, may arise through infection from the mouth-cavity and respiratory tract. When taken into the alimentary tract the poison becomes inactive as the result of changes produced by the digestive juices (see § 29).

The **tetanus-bacillus** is not isolated either in the earth or in infected wounds, and inoculations, therefore, consist of a mixture of bacteria. Attempts to isolate the bacillus by means of cultures were unsuccessful until the year 1889, when *Kitasato* succeeded by heating for a half-hour to one hour, on the water-bath, at 80° C. mixed cultures that had been kept for several days in the incubator, and then plating the cultures in an atmosphere of hydrogen. Through heat bacteria growing with the tetanus-bacilli were killed, while the latter survived. Tetanus toxin (*Kitasato*) is destroyed by heating (65° C. and over) for a few minutes and by direct sunlight (fifteen to eighteen hours), and also loses its virulence in a few weeks under the influence of diffuse daylight.

Literature.

(*Bacillus Tetani.*)

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§ 165. The **Bacillus** of malignant œdema (*Vibrion septique* of Pasteur) is an anaërobic bacillus present in various putrefying substances, and its spores are almost never absent from earth fertilized by decomposing fluids or liquid manure. The bacilli are 3–3.5 μ long, and 1–1.1 μ broad; they often form long pseudothreads. They resemble anthrax-bacilli, though somewhat more slender, and are rounded at the ends, not sharply cut across. In spore-formation a swelling of the rod takes place, as in the case of *Bacillus butyricus,* so that spindle- and tadpole-shaped forms arise.

The bacillus is motile, and possesses flagella on the ends as well as on the sides. It is not stained by Gram's method.

It grows in nutrient gelatin as well as in agar and coagulated blood-serum, but must be introduced deeply into the medium and protected from the air. Nutrient gelatin to which one to two per cent. of grape-sugar has been added is an especially favorable medium. Nutrient gelatin and blood-serum are liquefied, the latter with evolution of gas.

The bacillus can be obtained by sewing garden-earth under the skin of a guinea-pig, care being taken to prevent the access of air at the point of inoculation. The ensuing multiplication of the bacillus excites œdematous swelling of the subcutaneous tissue. At a later stage the bacilli spread over the serous membranes, and involve the spleen and other organs.

Mice, guinea-pigs, horses, donkeys, sheep, swine, cattle, and pigeons are susceptible to the bacilli; rabbits and fowls are less susceptible, while rats, dogs, and cats are still less so.

The bacilli of malignant œdema occasionally develop in the human body, particularly when the tissues are poorly nourished and the bacilli through accident — puncture of a hypodermic syringe — get into the deeper tissues. They excite gangrenous processes associated with hæmorrhagic œdema and gas-production.

As the **Bacillus phlegmones emphysematosæ** R. Fraenkel in 1892 described an anaërobic bacillus staining with Gram's method, that, in many cases, is to be regarded as the cause of phlegmonous inflammation associated with gas-formation. According to Fraenkel the bacillus is non-motile and only exceptionally forms spores. In cultures it forms gas. It occurs in the external world (by Fraenkel it was demonstrated on a splinter of wood with which a man dying of gas-phlegmon had been wounded); and when injected subcutaneously into guinea-pigs or sparrows produces a progressive gangrenous process with disintegration of the subcutaneous tissues and muscle, as well as free collections of fluid and gas. Intravenous injection into rabbits and guinea-pigs is followed by the formation of gas in the internal organs.

Fig. 415.—Bacillus pneumoniæ (Friedländer). *a*, Oval cells and rows of cells with gelatinous capsule; *b*, rod with gelatinous capsule. × 800.

Gas-phlegmon in man occurs most frequently after severe injuries, for example, compound fractures, but may also proceed from small wounds. The bacillus is found at times in company with other bacteria, pus-cocci, colon-bacilli; at other times alone and may be present in great numbers. In pure infections there occurs production of gas associated with liquefaction of tissue, particularly of muscles and of reticular connective tissue.

It is probable that this bacillus is identical with one described by Welch and Nuttall as *Bacillus aërogenes capsulatus.*

Besides Fraenkel's gas-bacillus other bacteria cause changes corresponding to those of gas-phlegmon and foamy organs, especially as the result of localization in an already infected tissue (lactic-acid-bacilli, proteus vulgaris, and colon-bacilli).

Literature.

(*Bacillus Œdematis Maligni. Bacillus Phlegmones Emphysematosæ.*)

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Simonds: Monographs of the Rockefeller Institute, 1915.
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§ 166. The **Bacillus pneumoniæ** (Friedländer) or Bacillus Mucosus Capsulatus, is plump, non-motile, without flagella, about 0.5–1.25 μ broad and 0.6–6.0 μ long. It forms no spores (Fig. 415). It belongs to the

group of **capsulated bacilli.** It is easily stained with aniline dyes, but is decolorized by Gram's method. It grows easily on the usual nutrient media, under both aërobic and anaërobic conditions, and does not liquefy gelatin. Stab cultures in gelatin show the so-called nail-culture, in that the bacteria growing over the stab-canal form a white mass of bacilli similar to a nail-head.

White mice and guinea-pigs are especially susceptible to the bacillus. The first named die within sixteen to forty-eight hours after subcutaneous inoculation. The point of inoculation and the regional lymph-nodes are inflamed and contain encapsulated bacilli, the latter are also found in the blood. Rabbits are almost immune to inoculation.

Friedländer and Frobenius, who first described the bacillus (1882),

Fig. 416.—Influenza-bacilli and pus-corpuscles, from sputum (fuchsin). × 1,000.

believed that it was the most frequent cause of croupous pneumonia, a view that may be explained by its confusion with the, at that time unknown, *Diplococcus pneumoniæ.* It is now recognized that it is rarely the cause of this disease (according to Weichselbaum, in about six per cent. of cases, according to Honl, in eight to ten per cent.); but it may cause focal pneumonia, pleuritis, pericarditis, pharyngitis, rhinitis, otitis media, and meningitis. In severe infections it can pass into the blood and set up metastases. In inflammatory exudates the bacilli are found in the form of rods and short oval cells surrounded by capsules, often forming chains (Fig. 415).

Capsule-bacilli similar to the pneumonia-bacillus are often found in the chronic inflammation of the nasal mucosa known as *ozæna,* which is characterized by a foul-smelling secretion and the formation of scabs; they have been demonstrated in *rhinoscleroma* (see below), and it has been assumed that they stand in causal relation to these diseases.

According to *Fricke* the bacterium of *Friedländer* is representative of a group of bacteria which are classed under the name *Bacillus mucosus capsulatus,* and represent varieties of a single species. The fission-fungus described as the ozena-bacillus is identical with the pneumonia-bacillus, probably also the bacillus from the milk-fæces of nurslings described as *Bacterium lactis aërogenes (Escherich).* It is possible that a greater etiological significance may be attached to it so far as the origin of many diarrhœas is concerned.

§ 167. The **influenza-bacillus** (Fig. 416) was described by R. Pfeiffer, in 1892; it is regarded as the cause of influenza. In influenza it is found in the catarrhal respiratory passages, occasionally in the lungs; the small bronchi may contain enormous numbers in pure culture. It is assumed that their multiplication in the respiratory tract gives rise to inflammation, and that the bacilli produce poisons, which, when absorbed, cause the symptoms of influenza.

Influenza-bacilli are small, thin rods with rounded ends (Fig. 416), separate or joined in twos. They stain with ordinary aniline dyes, but not by Gram's method. They may be cultivated at body-temperature on blood-agar on which they form small, dew-like colonies. The nutrient medium must contain hæmoglobin. Spore-formation has not been observed. In apes catarrhal inflammation of the respiratory tract may be produced by intratracheal injections of pure cultures.

In 1918 a disease popularly known as **influenza** swept around the world, killing hundreds of thousands. It was characterized by a variety of pneumonia of abrupt onset and amazingly rapid course. Death not infrequently occurred in 24 or 36 hours, or within a week at the latest. The pneumonic lesions were bilateral in distribution, involved the bases of the lungs most frequently, and were lobular in type, confluence of the solidified lobules, giving rise to extensive areas of consolidation. The exudate was composed largely of red cells and exuded blood serum, together with polynuclear leucocytes. Interstitial, parenchymatous and pleural hæmorrhages were almost constant. The pleura, in the majority of cases, was not involved by the inflammatory process. Areas of acute vesicular emphysema were common and rupture was sometimes followed by extensive subcutaneous infiltration of air. The naked eye and histological appearances of the lungs bore a striking resemblance to those of bubonic plague. Bacteriologically, the findings varied greatly, and the cause of the disease is still in doubt. Influenza bacilli, hæmolytic streptococci, pneumococci and other micro-organisms were to be found in the lungs in pure culture or in various combinations. The kidneys, in most cases, presented marked evidences of acute parenchymatous degeneration. In some instances, the rectus muscles were the seat of Zenker's degeneration associated with hæmorrhagic extravasation, occasionally ending in secondary infection and abscess formation.

About a year later the same variety of disease recurred in various parts of the world, but in milder form. Pneumonia was relatively rare and its course was more prolonged. The anatomical changes in the lungs were extremely variable, but conformed in a general way to the confluent lobular hæmorrhagic and exudative pneumonia of the pandemic year. Pulmonary and subpleural abscesses were frequent. The pleura was involved in the majority of cases and empyemata were common. The interlobar and interlobular pleural extensions were often richly infiltrated by inflammatory exudate. Recovery from the pneumonia was commonly followed by sequelae in the form of persistence of pulmonary abscesses, empyemata, and

FIG. 417.—Diphtheria-bacilli from a pure culture. Streak preparation (methylene-blue). × 1,000.

organization of the pleura and its intrapulmonary prolongations. (Blanton and Irons, Jour. Amer. Med. Assn., 1918; Symmers, New York Med. Jour., 1918; Jour. Amer. Med. Assn., 1918.)

According to Czaplewski and Hensel and Koplik (Centralbl. f. Bakt., 1897), there is found in the respiratory tract in **whooping-cough** a small, non-motile **bacillus** similar to the influenza-bacillus, that is thought to be the cause of whooping-cough. Later investigations have shown that bacilli of the same type are to be found in the respiratory mucous membranes in a variety of conditions. Their significance is highly doubtful.

§ 168. The **Bacillus diphtheriæ** (Fig. 417) is found in the croupous membrane in diphtheria, and is the cause of this disease.

The bacilli are 1.5–3 μ long, and are often somewhat swollen at the ends. In cultures they form rods of varying length (Fig. —), the ends of which are often clubbed. When stained the bacilli appear spotted or granular. They stain best in a solution of 30 c.c. of concentrated alcoholic methylene-blue in 100 c.c. of 0.0001 per cent. potassium hydroxide, after which the sections are treated for a few seconds in 0.5 per cent. acetic acid and then with alcohol. In stained preparations the bacilli often appear segmented. They also stain by Gram's method, provided treatment with Lugol's solution and alcohol is brief.

Diphtheria-bacilli grow best in the presence of oxygen on a mixture of three parts of calf's or sheep's serum, and one part of neutralized veal-bouillon, to which one per cent. of peptone, one per cent. of grape-sugar, and 0.5 per cent. of common salt are added; or on blood-serum and agar with an addition of ten per cent. glycerin or of sugar-containing bouillon. They form grayish-white colonies. For development they need

a temperature above 20° C.; they grow best at 33°–37° C. They are resistant to drying; but may be quickly killed by moist heat. Spore-formation has not been observed.

Guinea-pigs inoculated subcutaneously with cultures of diphtheria-bacilli die in two to three days. Hæmorrhagic œdema is found at the point of inoculation. The inoculation-area contains bacilli, the internal organs, on the contrary, are free, although the adrenals are intensely injected or even hæmorrhagic. The *introduction of cultures into the trachea* of rabbits, chickens, and pigeons, as well as *inoculation of the conjunctiva of rabbits* and the *vagina of guinea-pigs* is followed by inflammation with the formation of a pseudomembrane. Sheep, horses, cats, dogs, cows, rabbits, and pigeons are susceptible to subcutaneous inoculation. Rats and white mice are nearly immune.

Roux, Yersin, Löffler, Spronck, and others observed paralysis in pigeons and guinea-pigs surviving inoculation. Roux and Yersin assert that the intravenous injection of filtered bouillon-cultures free from bacteria will cause in guinea-pigs and rabbits after two to three days paralysis and death.

The virulence of cultures varies greatly. Diphtheria bacilli produce in the human body and in cultures **toxins,** which may be precipitated by alcohol as a whitish powder.

Water-solutions of the poison injected subcutaneously into animals cause local necrosis, hæmorrhagic œdema, and inflammation; when taken into the body-juices they give rise to pleural effusions, nephritis, fatty degeneration of the liver, and paralysis.

Diphtheria in man is characterized by inflammation involving the mucous membrane of the pharynx, palate, arch of the palate, and upper respiratory passages, sometimes localized areas of skin. It appears as a *febrile disease associated with symptoms of intoxication* and gives rise to localized *croupous exudations,* and to sloughing (cf. § 91, Figs. —, —). The croupous membranes constitute the most striking feature of the disease; they are found in the throat and nose in the form of patches; or they may form a continuous layer lining the larynx and trachea, or even the bronchi. Beneath the croupous membrane the epithelium is lost; and the connective tissue is hyperæmic, infiltrated, and swollen (Fig. —). In severe cases the superficial layers of the connective tissue are necrotic. Of the deeper tissues the regional lymph-nodes often reveal, microscopically, foci of necrosis. Of the internal organs the kidneys may show changes, in the form of fatty degeneration of the epithelium and of the cells of the capillary walls; not infrequently they also present focal areas of small-cell infiltration. In the spleen there are frequently found necroses of the lymphoid follicles. Degenerative changes and areas of inflammation not infrequently occur in the heart-muscle. Paralyses are caused by degeneration and necrosis (Katz) of the ganglion-cells of the medulla oblongata and of the spinal cord and of the corresponding nerves.

The lungs are not demonstrably changed by the diphtheria poison itself, but pneumonia, due to aspiration of irritating bronchial contents or to extension of inflammation to the pulmonary parenchyma, is of frequent occurrence.

Local inflammations of mucous membranes as well as *symptoms of intoxication may be caused by diphtheria bacilli and their toxins;* but it must be noted that *streptococci* are almost regularly present in the diseased area, and that a *pure streptococcus infection* may present the

clinical and anatomical picture of *"diphtheria."* When both micro-organisms are present the injurious effect of one may be supplemented by that of the other; the presence of streptococci appears to increase the virulence of diphtheria bacilli. In severe forms of diphtheria streptococci are usually present in numbers; nevertheless streptococcus infection does not warrant a bad prognosis, since the virulence of the cocci varies greatly.

In the course of infection with diphtheria bacilli there arise *anti-toxins,* which nullify the action of the toxins, and aid recovery. The formation of antitoxins follows inoculation of animals with attenuated bacilli, and on this rests the possibility of obtaining from animals (sheep, horses), that have been repeatedly inoculated with bacilli of increasing virulence, a serum which contains antitoxin of therapeutic value (cf. § 32).

There are frequently present in the mouth and throat bacilli, which are designated **pseudo-diphtheria bacilli.** Since diphtheria-bacilli may lose their virulence, it is not impossible that both forms represent varieties of the same species.

§ 169. The **bacillus of bubonic plague (Bacillus pestis)** was discovered in 1894 by Kitasato and Yersin, of the Japanese and French commission, while investigating an epidemic in Hong-Kong. The pest-bacillus is a small rod with rounded ends (resembling the bacillus of chicken-cholera). It stains with aniline dyes, especially well with methylene-blue, and shows exquisite polar staining (Fig. 418). It is decolorized by Gram's method. It is found in all cases of plague, in abundance in the swollen lymph-nodes, but also in the spleen and blood. It may be cultivated on various media, and forms bluish-gray colonies. It multiplies abundantly in bouillon containing sugar, and forms toxins. Inde-

FIG. 418.—Plague bacilli (fuchsin). × 580.

pendent movements have not been observed. Spores are not formed. The bacilli are easily killed by warming, but are able to withstand drying.

Bubonic plague, which destroyed great numbers of the inhabitants of Europe, at the close of the seventeenth and beginning of the eighteenth centuries ("Black Death"), has disappeared from Europe. In Asia (Yunnan in China, Arabia, Mesopotamia), and in the interior of Africa the disease seems to be endemic, and spreads from time to time in the same manner as cholera.

Man is infected usually through the skin, more rarely from the mucous membrane of the mouth, nose, throat, and conjunctiva, still more rarely from the deeper parts of the respiratory tract, although cases of primary pest-bronchitis and pest-pneumonia occur. Small wounds usually form the avenue of entrance in the skin, but it appears (Albrecht and Ghon) that rubbing of the skin with infected fingers or clothing may be sufficient to bring about infection.

The bacilli are taken up by the lymph-vessels and deposited in the regional lymph-nodes, where they cause marked swelling of the infected node or group — the *primary bubo.* Through infection of lymph-nodes

situated farther along the lymph-system there arise *primary buboes of the second class,* and by metastasis through the blood-stream *secondary buboes* are formed. The plague is thus characterized by an *acute polyadenitis.* Since the poisons which are in association with the bodies of the pest-bacilli exert a degenerative and necrotic effect on the vessel-walls, numerous *hæmorrhages* are caused; these are absent only in rare cases. To these changes there are also added circumscribed foci in the spleen, liver, kidneys, lungs, skin, etc. With the exception, therefore, of those rare cases in which pest-infection is confined to the primary bubo, the disease is to be regarded as a *general infection* which arises from the taking-up of bacteria from a primary focus of infection, and runs its course with the clinical picture of *polyadenitis* and *hæmorrhagic septicæmia.*

The individual foci are characterized by areas of *coagulation-necrosis, inflammation,* and *hæmorrhage,* and are caused by the presence of extraordinarily large numbers of bacilli. The lymph-nodes of the primary bubo are hæmorrhagic, swollen and of medullary consistence. After a few days they also show yellow necrotic areas which later undergo liquefaction. When the disease has lasted longer than six days, the liquefaction of lymph-nodes may take on the character of *suppuration.*

The tissues in the neighborhood of the lymph-nodes are œdematous and infiltrated with blood; hæmorrhages are also found in the walls of the neighboring large veins.

The secondary inflammations of the lymph-nodes and of the lymph-adenoid tissue of the mouth and throat do not usually cause such a marked degree of swelling as do the primary; they resemble the medullary swelling in typhoid fever. The surrounding tissues are also less changed, but if the process be prolonged the picture comes to resemble that of the primary buboes.

The spleen of plague-patients is somewhat swollen, dark red, finely granular, shagreened, and often contains small necrotic foci, which are caused by the development of bacilli in great numbers.

In the glandular organs and skin, there occur, besides hæmorrhages, necrotic areas and exudative inflammations, all due to the presence of bacilli. In the lungs there may occur, in addition to the primary pest-pneumonia, secondary metastatic focal inflammations and aspiration-bronchopneumonias.

The majority of individuals infected with pest die within the first eight days, but others may live several weeks and then die of marasmus.

Not infrequently *secondary infections,* particularly by streptococci and diplococci, are associated with the pest-infection. They arise chiefly in the tonsils and follicular glands of the tongue following changes caused by the pest-bacilli.

Among *animals, rats, mice, apes,* and *cats are especially susceptible to pest;* in rats, spontaneous infections occur, so that these rodents aid in the spread of epidemics. Swine and dogs are less susceptible, birds still less so.

The changes in infected animals agree in general with those observed in man. The infection may remain local or become general. After lymphadenitis and multiple hæmorrhages there arise miliary, tubercle-like foci in the spleen, liver, and lungs. The course is usually acute, rarely chronic. In the latter case the larger necrotic foci may be encapsulated by connective tissue. The animals are easily infected from the skin, as

well as from the mucous membranes of the intestinal and respiratory tracts; infection may take place from an uninjured mucous membrane. The inoculation of one mouse confined in a cage with other mice may give rise to a cage-epidemic (Schottelius).

Attempts to *immunize animals and man against pest by means of dead and attenuated pest-bacilli* have been many times carried out, especially by *Yersin, Haffkin,* and *Lustig;* and have been successful in so far that rodents, horses, and apes have been rendered immune against inoculations otherwise fatal. According to the reports of such attempts in man, a smaller per cent. of inoculated individuals acquire the disease than of those not inoculated; but doubt is thrown upon the results of these inoculations by other authors (*Bitter*). Further, *attempts at immunization and healing have been made in man, with the serum of animals which have been rendered immune,* particularly of horses (*Yersin, Lustig*); and different authors ascribe to such serum a favorable influence.

Sticker differentiates the following forms of pest according to the first localization of the bacilli: (1) Bubonic plague (the most common form); (2) the cutaneous form (formation of vesicles and ulcers or furuncle-like inflammations); (3) the pulmonary form; (4) the intestinal form.

Through the investigations of *Ducrey, Krefting,* and *Petersen* (cf. *Petersen,* "Ulcus Molle." *Arch. f. Derm.,* xxix., 1894; xxx., 1895, and *Babes,* "Handbuch d. pathog. Mikroorg., iii., 1903) it is probable that *ulcus molle* or *soft chancre* is caused by a bacillus. *Tomasczewski* ("Der Erreger des Ulcus," *Z. f. Hyg.,* 42 Bd., 1903) has demonstrated through self-inoculation that typical ulcus molle can be produced with cultures grown on blood-agar or blood. The bacillus is non-motile, does not stain with Gram's method, and often forms chains. (See also "Observations on the Distribution and Culture of the Chancroid Bacillus," by *Davis, Jour. of Med. Res.,* 1902).

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§ 170. The **Bacillus tuberculosis** is the cause of the infectious disease occurring so frequently in man and the domestic animals which is known as **tuberculosis,** sometimes called *pearl disease* in animals.

The tubercle-bacillus was discovered and thoroughly studied by Koch in 1882. It is a slender rod (Fig. 419), of 1.5–4 μ in length, and is usually slightly curved. It may be stained by aniline-dyes (fuchsin, gentian-violet) to an aqueous solution of which an alkali, or carbolic acid, or aniline oil is added. The bacilli when once stained retain the stain, even when the preparation is decolorized in dilute sulphuric acid, or nitric acid, or hydrochloric acid and alcohol.

The stained bacilli not infrequently show in their interior clear, shining, unstained areas, or are composed of little stained spherules. Koch regarded these clear spots as spores, and this view was accepted for a long time. Nevertheless, germination of these structures could not be demonstrated, and they are no longer regarded as spores. Consequently,

tubercle-bacilli are not specially resistant forms, although they are more resistant to external influences, for example, drying, than are many other bacteria.

Tubercle-bacilli may be cultivated at the body temperature and in the presence of oxygen on coagulated blood-serum, blood-serum-gelatin, agar to which rabbits' blood has been added, and in glycerin bouillon. The special medium devised by Petroff is excellent. They increase, however, very slowly, so that only on the seventh to tenth day or even later, do the cultures become visible in the form of dull-white flakes resembling little scales. Larger cultures form, on the surface of coagulated blood-serum, whitish, irregularly shaped, lustreless deposits. According to Nocard, Roux, and Bischoff growth of the bacilli is aided by the addition of glycerin (four to eight per cent.). In cultures tubercle-bacilli form threads, which in part show branching.

At temperatures below 28° C. and above 42° C. the growth of the bacilli ceases. Sunlight kills the bacilli in a short time.

If bacilli from pure cultures are inoculated into certain experimental animals, tuberculosis is produced; infection may be produced by inoculation under the skin, into the peritoneal cavity, or the anterior chamber of the eye, by inhalation of an atomized suspension, by feeding, and by injection into veins. In experimental feeding success is often attained only after long administration of the bacilli, since not every bacillus gaining entrance into the intestinal tract leads to infection. It is also true that bacilli lodging on the mucous membrane of the respiratory tract do not always succeed in growing in the tissue. Guinea-pigs, rabbits, cats, and gray field mice are especially susceptible; dogs, rats, and white mice less so.

Fig. 419.—Tubercle-bacilli. Sputum from a man suffering with pulmonary tuberculosis. Smear-preparation on cover-glass, stained with fuchsin and methylene-blue. × 400.

Infection of man and of animals occurs from the taking up of tubercle-bacilli from the lungs, respiratory passages, and the intestinal tract, or from wounds and tissue-ulcerations. In the alimentary tract, the lymph-adenoid apparatus, tonsils, and the intestinal lymph-follicles form the most frequent avenue of entrance. Nurslings are particularly susceptible to intestinal infection.

The opinion seems to be held by certain surgeons that primary or so-called surgical tuberculosis of the intestine is a not uncommon occurrence, and, based on this opinion, extensive resections have actually been carried out. Anatomically, there are two well recognized varieties of intestinal tuberculosis. One of them invites surgical interference. This lesion is a chronic productive tuberculous inflammation, usually located in the region of the cæcum and often involving a large portion of the ileum. It produces massive thickening of the intestinal wall and obstruction or even occlusion of the lumen. Three such cases were encountered among approximately 30,000 surgical specimens examined at Bellevue Hospital. The second variety of surgical intestinal tuberculosis consists in solitary or multiple, discrete or confluent, tuberculous ulcers corresponding, as a rule, to the distribution of the lympoid tissues of the gut. Among 6,000 consecutive autopsies at Bellevue Hospital, Palinsky (Proceedings New York Path. Soc., 1919) found 285 cases of tuberculous enteritis (46 per cent.). Of this number, however, only 3 (1 per cent.) were unaccompanied by tuberculous lesions in other portions of the

body. In 37 per cent. of all cases of intestinal tuberculosis, more than one part of the gut was found to be involved. Not infrequently the ulcerative lesions occupied both the colon and the small intestine. It is apparent, therefore, that primary intestinal tuberculosis is an extremely rare condition and that operative removal of any portion of the gut for tuberculosis should be approached with caution.

Direct transmission of the bacilli from mother to *fœtus in utero* may occur, but is rare. The production of tuberculosis occurs usually at the points of entrance of the bacilli, but may occur at distant points after transportation of bacilli through the blood or lymph, so that hæmatogenous or lymphogenous disease of the internal organs, for example, of the lymph-nodes, bones, brain, and tubes, may occur as the primary localization.

The bacilli are spread through the e x t e r n a l world chiefly by sputa, under certain conditions by the fæces and urine, from tuberculous ulcers, or from tuberculous organs taken from living or dead persons. Since the bacilli are rather resistant, they may be preserved outside the animal body for a long time under certain conditions, and may become mixed with the respired air, as well as with food and drink. The milk of tuberculous cows con-

FIG. 420.—Tubercle from a fungous granulation of bone (Müller's fluid, Bismarck brown). *a*, Giant-cell; *b*, epithelioid cells; *c*, lymphoid cells. × 400.

tains the bacilli, especially when the udder is diseased; but bacilli may also pass into the milk when no disease of the udder can be demonstrated (Hirschberg, Ernst, Leuch).

If tubercle bacilli succeed in developing in any tissue of the human body, they lead by a series of changes to the formation of *nodular masses of fibroblastic tissue* or **tubercles,** which are devoid of *blood-vessels,* and after reaching a certain stage of development undergo retrogressive changes. The formation of the nodule may be accompanied by more or less extensive inflammatory exudation.

The first effect of the development of the bacilli in tissue is *degeneration,* in which the tissue-cells as well as the connective-tissue ground-substance over a larger or smaller area are destroyed. To the degenerative processes there is added inflammatory exudation — *emigration of leucocytes and lymphocytes* — and *proliferation of the tissue-cells that remain preserved* in the affected area (Fig. 420, *a*). The degree of the exudative processes in the region of the nodule varies and is dependent on the number and virulence of the bacilli present and on the mode of infection. When a large number of bacilli are introduced into the lung through the

respiratory tract the exudative inflammation is pronounced. It is *less* marked in the introduction of bacilli into the liver through the portal vein.

The *cells of the exudate* are chiefly *polynuclear leucocytes,* but later *mononuclear lymphocytes and leucocytes* predominate. The *appearances* of *proliferation* may be shown by the second day.

The *cellular nodule* which, after a few days represents the tubercle at
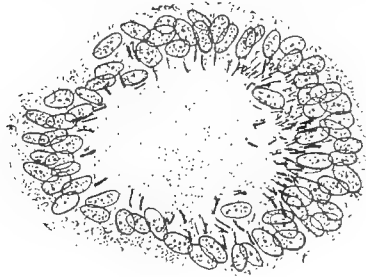
FIG. 421.—Giant-cell containing bacilli, and showing necrotic centre, from a tubercle. Stained with gentian-violet and vesuvin, mounted in Canada balsam. × 350.

the height of its development, usually shows three types of cells — *large epithelioid cells, with clear nuclei* (Fig. 420, *b*), *multinuclear giant-cells* (*a*), and *lymphocytes* (*c*). The first two are found particularly in the central part of the tubercle, the latter at the periphery. The number of the individual cell-forms varies, and under certain conditions the lympho-
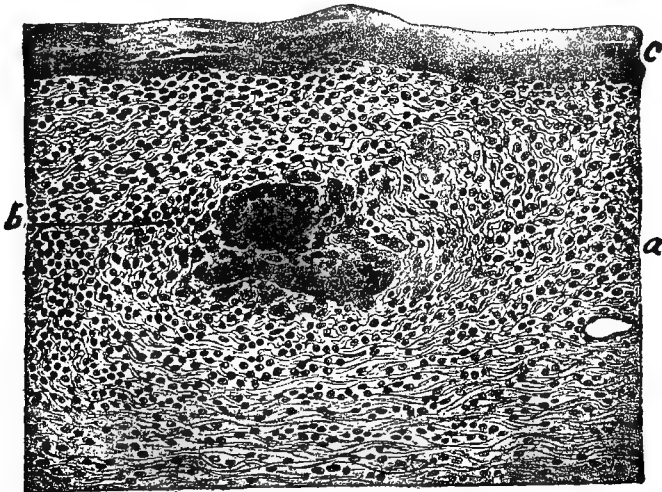
FIG. 422.—Tuberculosis of the pleura (alcohol, Van Gieson's). *a,* Thickened and proliferating pleura; *b,* tubercle with giant-cells; *c,* deposit of fibrin. × 200.

cytes may be so numerous as to overshadow the larger cell-forms. At other times epithelioid cells with lightly staining nuclei predominate. These cells are in part changed lymphocytes arising from the blood; in part fibroblasts arising through proliferation of connective-tissue cells *in loco.*

The giant-cells belong usually to the syncytial type and arise through confluence of cells, it is also possible that they arise through the multiplication of the nucleus in a single cell. The nuclei lie usually in the peri-
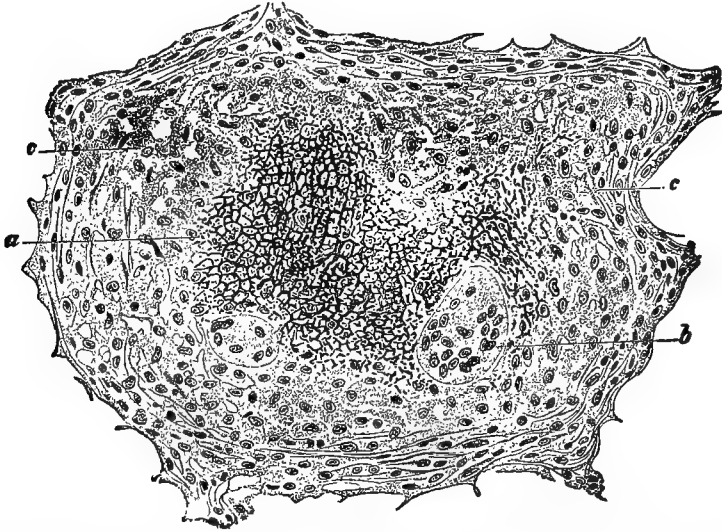
FIG. 423.—Large-cell tubercle containing fibrin, from a tuberculous lung (alcohol, fibrin-stain). *a*, Fibrin; *b*, giant-cell; *c*, large-cell tissue. × 300.

pheral portion of the protoplasmic mass (Figs. 420, *a* and 421); sometimes collected at one pole, sometimes at both poles; sometimes arranged in a wreath or crescent. They often contain bacilli (Figs. 421 and 424, *c*). The non-nucleated portion of the protoplasm may often be recognized as degenerate or necrotic because of its re-action toward stains (Fig. 421).

Through proliferation of cells the connective-tissue stroma of the original tissue is pushed farther and farther apart, so that the individual cells are finally separated from one another only by scanty fibres, whose general arrangement in the form of a network is consequently called the *reticulum of the tubercle.*

New vessels are not formed in the tubercle; and *old vessels are closed through proliferation of the vessel-walls.* Usually the *new-formation of connective tissue stops with the production of fibroblasts.*

FIG. 424.—Caseous necrosis of tuberculous granulation tissue (alcohol, fuchsin, aniline blue). *a*, Granular, *a₁*, lumpy caseous masses; *b*, fibrocellular tissue; *c*, giant-cell with bacilli; *d*, bacilli in cellular tissue; *e*, bacilli in necrotic tissue; *f*, bacilli enclosed in cells. × 200.

The neighborhood of the tubercle may show no essential change, but usually presents small-cell infiltration or proliferation (Fig. 422, *a*).

Serous exudation is usually associated with the cellular emigration, and *fibrin* may be formed both *in the tubercle itself* (Fig. 423, *a*) and *in its neighborhood* (Fig. 422, *c*).

At the height of development the tubercle forms a small, *gray, translucent cellular nodule,* which may reach the size of a millet-seed, and encloses in its tissue tubercle-bacilli in larger or smaller numbers. When it has reached a certain size *retrogressive changes* usually appear in its centre, the tubercle becoming cloudy, opaque, and of a white or *grayish-white* or *yellowish-white color* — these changes are designated caseation.

Caseation of the tubercle is dependent on *necrobiosis of cells,* and on the *deposit of coagulated substances* between the cells. The cell-necrosis is characterized by loss of nuclei and transformation of the cells into lumpy masses which disintegrate and become granular (Fig. 424, a_1, a). The deposit between the cells consists of a network of fibrin (Fig. 423, a) or of a granular or hyaline reticulated fibrinoid substance
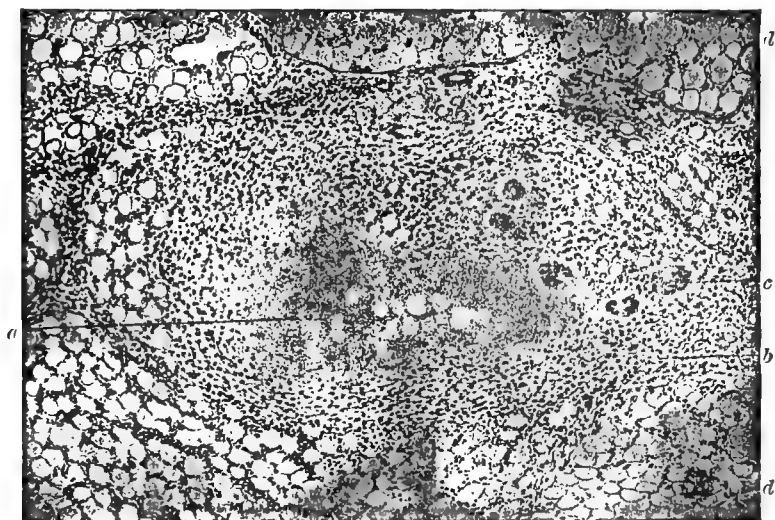
FIG. 425.—Section of miliary tubercle of the omentum (alcohol, hæmatoxylin, eosin). *a*, Caseous centre containing remains of fat-cells; *b*, fibrocellular periphery; *c*, giant-cells; *d*, fat tissue. × 100.

but which does not take Weigert's fibrin stain and is stained yellow by Van Gieson's method. In the further course of the process of caseation the fibrin and fibrinoid substance disintegrate into a granular mass which fuses with the cell-detritus (Figs. 424, *a;* 426, *a*).

Caseation affects first the central portion of the tubercle, and is usually confined to this, while connective tissue is formed at the periphery, so that the *tubercle* comes to consist of a *caseous centre* (Fig. 425, *a*) and a *fibrocellular periphery* (*b*) which usually contains *giant-cells.* Under certain conditions caseation may involve the entire tubercle. If caseation does not affect the periphery, the fibrocellular tissue of the peripheral zone, sooner or later, becomes transformed into pure *fibrous tissue,* a **fibrocaseous tubercle** (Fig. 426, *a, b*) is formed, the connective tissue of which is coarsely fibrillar or hyaline and poor in cells (*b*), and in the course of time usually becomes sharply defined from the caseous centre (*a*), so that the latter appears to be encapsulated. If the disease runs a favorable course the centre instead of caseating may undergo connective-tissue replacement, and (Fig. 427, *b, c, d*), the tubercle becomes changed into a **fibrous nodule.**

The *infectious nature* of *tuberculosis* was determined by experimental transmission of tuberculosis to animals (*Villemin, Lebert, Wyss, Cohnheim, Klebs, Langhans,* and others), before the discovery of the tubercle-bacillus. Nevertheless, it was a long time before the view that tuberculosis is an infectious disease received general acceptance, and opposition to this view has even to-day not wholly disappeared.

The peculiar behavior of the tubercle-bacillus toward stains — that is, its property of retaining the stain after treatment of the preparation with acids and alcohol, the so-called *acid-* and *alcohol-resistance* — makes it possible to demonstrate tubercle-bacilli in the sputum or in tissues, and to differentiate it from other bacteria. It should be noted, however, that other bacteria show these properties; the *bacillus of leprosy,* the *smegma-bacillus* (a bacillus frequently found on the corona glandis, between the scrotum and thigh and in the folds between the labia majora and minora), two *bacilli found in butter* (one described by *L. Rabinowitsch* and *Petri,* the other by *Korn*), and finally different bacilli cultivated by *Moeller* from *grasses* (timothy-grass) and from *cow-dung.* All these acid-resisting bacilli
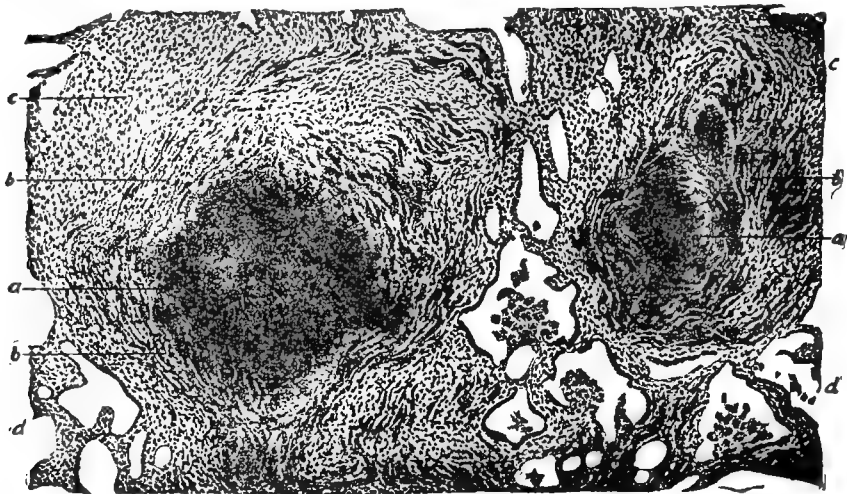
Fig. 426.—Fibrocaseous tubercle of the lung (alcohol, Van Gieson's). *a,* Caseous centre; *b,* thick, homogeneous connective tissue poor in nuclei; *c,* connective tissue rich in cells; *d,* lung tissue. × 80.

may under certain conditions lead to errors of diagnosis; for example, the smegma-bacillus in the examination of urine, the butter-bacilli in the examination of butter, the latter particularly, since the bacillus described by *Rabinowitsch,* when injected into the peritoneal cavity of guinea-pigs, causes a disease of the abdomen similar to true inoculation-tuberculosis, while the bacillus described by *Korn* causes pseudo-tuberculosis in white mice (these animals showing but slight suceptibility to true tuberculosis). Acid-fast bacilli, which probably represent a variety of the Rabinowitsch butter bacillus, have been found in gangrenous foci in the lung (*Rabinowitsch*) as well as in the sputum of pulmonary gangrene (*Folli, Mayer, Ophüls, Birt* and *Leishman*). *Moeller* has found acid-fast bacilli in nasal and pharyngeal mucus.

Since the tubercle-bacillus in cultures forms simple and branching threads (*Klein, Fischel, Coppen-Jones, Nocard, Maffucci,* and others) and bud- and club-like swellings, many authors are inclined to group it with the thread-fungi. *Lehmann* and *Newmann* designate it as *Mycobacterium tuberculosis, Coppen-Jones* as *Tuberculomyces.*

Since the tubercle-bacillus in caseous pulmonary foci (*Coppen-Jones*), and after direct injection into the parenchyma of the brain, kidneys, mammary glands, and testicles, as well as after the intra-arterial injection of large numbers of bacilli (*Babes, Levaditi, Schulze, Lubarsch, Friedrich,* and *Nösske*) forms, in addition to the ordinary colonies of bacilli, fungus-masses resembling those of actinomyces, on

the outer surface of which ray-like clubs radiate into the surrounding tissue, *Lubarsch* and others, on the assumption that the fungus-masses consist of branching threads, have classed the tubercle bacillus with the actinomyces or ray-fungi. *Lubarsch* regards the ray-fungi as a sub-class of the *Streptothrices,* an intermediate group between the *Schizomycetes* and the *Hyphomycetes,* and characterized by the formation of clubs; and to this class he assigns the butter- and dung-fungi mentioned above. According to *Friedrich* and *Nösske* the fungus-masses regarded as resembling those of actinomyces consist only of rods.

According to the investigations of *Hammerschlag, Ruppel, Sata,* and others, tubercle-bacilli contain an abundance of fat, which under proper conditions may be demonstrated by staining with sudan (Sata). According to *Hammerschlag* tubercle-bacilli contain twenty-seven per cent. of substances soluble in alcohol and ether (fats, lecithin, poisonous substances), while other bacteria contain only 1.7-10 per cent. of the same. The remaining substance insoluble in alcohol contains albumin and cellulose. Apparently the acid resistance of the bacilli is dependent on the rich fat content; young bacilli which lack the fat covering are not acid-fast (*Marmorek*).
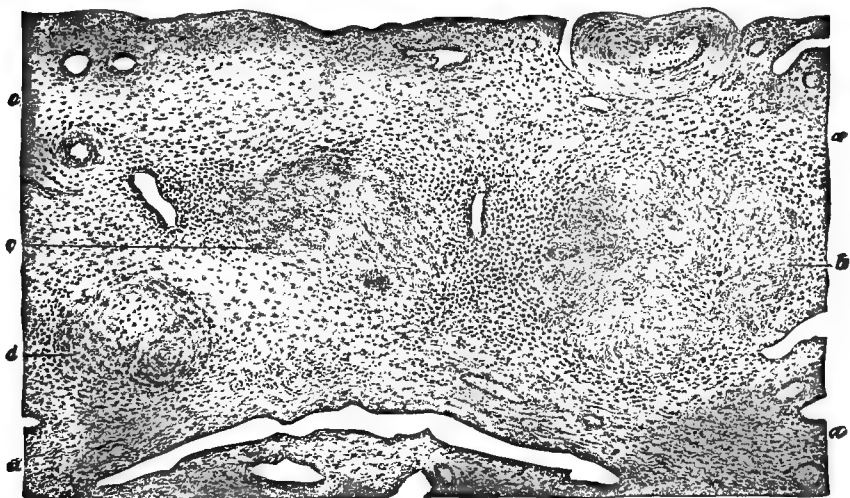
FIG. 427.—Fibrous tubercle in the thickened synovial membrane of the knee-joint (alcohol, hæmatoxylin, picric acid, fuchsin). *a,* Connective tissue; *b, c, d,* fibrous tubercle. × 75.

According to the investigations of *Prudden, Hodenpyl, Kostenitsch, Vissmann, Masur, Kickel,* and others, dead tubercle-bacilli, when introduced into the tissues of an animal by inoculation, or into the blood-stream, or through introduction into the respiratory passages, excite, at the point of deposit, inflammation and tissue-proliferation similar to that caused by living bacilli, and in the case of a large inoculation may lead to suppuration. These changes differ, however, from those produced by living bacilli, in that the bacilli are destroyed after a few weeks and the nodules heal through transformation into fibrous tissue; and by the fact that the severity of the local tissue-proliferation is dependent wholly on the amount of dead bacilli introduced, and that there is no spread of the process throughout the body. The dead bacilli must therefore contain substances (proteins) which cause inflammation and later tissue-proliferation.

The *active substance of the bodies of the bacilli — tuberculin —* was first produced by *Koch* (1890) from six- to eight-weeks-old cultures in a weak alkaline veal-infusion, to which one per cent. of peptone and four to five per cent. of glycerin were added, by evaporation on a water-bath to one-tenth of the original volume and filtering through a filter of earthenware and silicious marl. Later (1897) he dried highly virulent cultures of tubercle-bacilli in a vacuum-exsiccator, then triturated the dry substance, mixed it with distilled water and centrifugated it. The active principle is in the muddy precipitate thus obtained, which is again dried and triturated and dissolved in water to which twenty per cent. of glycerin

is added for the purpose of preservation.   This tuberculin (designated by Koch as T. R.) is said to contain 10 mgm. of solid substance in 1 c.c.

Whether tubercle-bacilli produce a true *toxin* is a question that has not yet been decided, but this is probably not the case; in favor of this is the fact that localized tuberculosis clinically shows no symptoms of intoxication.   The *tuberculins* obtained by various methods contain a *mixture of different substances* which, like the substances derived from other bacteria, excite inflammation.   Perhaps they contain also specific albumin bodies which, in the organism, cause the production of specific *bactericidal protective forces,* either through the formation of *bacteriolysins* or of *agglutinins* and *precipitins* that act on bacteria.   (See § 33.)

Through the investigations of *Arloing* and *Courmont* we know that an emulsion *of tubercle-bacilli* grown on potatoes is agglutinated by the serum of tuberculous men and animals.   Through a special method *Koch* has prepared a fluid containing bacilli in which clouding and a flocculent precipitate is produced by an
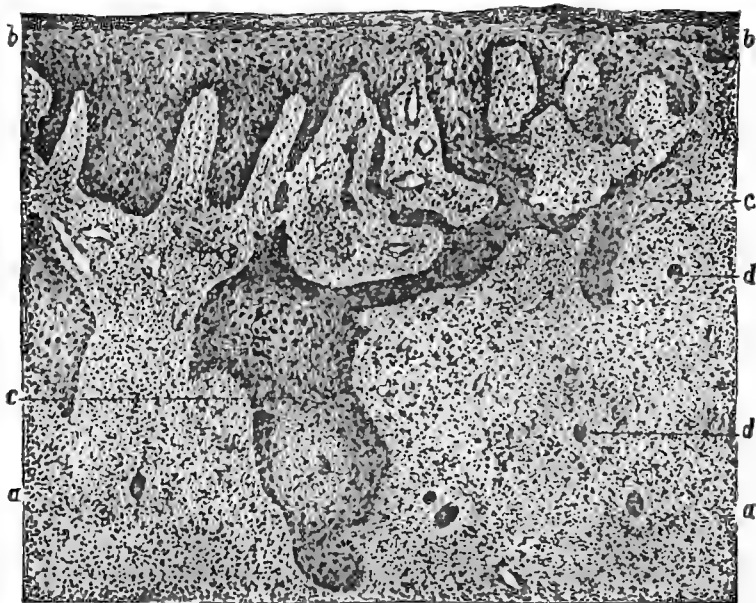
Fɪɢ. 428.—Lupus of the skin with atypical growth of epithelium, from the region of the knee (alcohol, hæmatoxylin, fuchsin, picric acid). *a,* Corium converted into granulation tissue in which there are scattered tubercles; *b,* epidermis; *c,* epithelial plugs growing into the deeper tissues; *d,* tubercle. × 50.

agglutinating serum.   The serum of healthy animals (rabbits, dogs, cow, and donkey) shows no agglutinating action when the test fluid is added to the serum in the proportion of 1:25; yet there are exceptions to this, and horse serum usually shows an agglutinative power.   According to *Koch* and *Romberg* the serum of children possesses no agglutinative power.   After the fourteenth year it is frequently present, probably as the result of latent tuberculosis.   Through treatment of an animal with dead or living cultures of tubercle-bacilli it is possible to produce a serum capable of agglutination (*Koch*) or to increase that already present, particularly easily in goats and donkeys.

Animals possessing the *power of agglutination* show a more or less high degree of *immunity against artificial infection with tubercle-bacilli,* and the agglutinative power may therefore be regarded as an indication of the existence of protective substances.

In men suffering from tuberculosis the power to agglutinate is not usually shown in dilutions of 1:25.   In advanced tuberculosis the agglutination power is usually wanting, since in the course of malignant tuberculosis the protective substances are either not formed at all or at least only in small amounts.   A mixture of pulverized tubercle-bacilli in 100 parts of water plus 100 parts of glycerin when

injected in increasing doses (0.8 per cent. salt solution, the first dose contains 0.0025 mg. of the cell substance of the bacilli) has, in the hands of *Koch*, increased the agglutination power of numerous consumptives (from 1 :25 to 1 :100 and 1 :300), so that it may be assumed *that it is also possible to produce in consumptives a certain amount of protective substance.*

As to the *value of the old and new tuberculin of Koch* writers differ. Its worth as a *diagnostic aid* is not questioned, particularly the old tuberculin, since small doses excite fever in tuberculous animals but not in healthy ones, yet there are exceptions to this. The old tuberculin finds use in the recognition and removal of tuberculous domestic animals. As a curative method (it is used in small doses in tuberculosis) it is praised by some, but at present its use is not extensive.

Much clinical interest has been excited over the diagnostic use of tuberculin in the *cutaneous reaction* ("*Pirquet's reaction*") and the *conjunctival reaction* ("*Calmette's reaction*").

Von Behring has succeeded in rendering cattle immune against virulent bovine tubercle-bacilli. He uses first cultures of human tubercle-bacilli which are less virulent for cattle, and begins with an intravenous injection of 1 mgm. of a serum-culture of a definite strength of infection. In younger animals the immunization is more easily produced than in older ones. *Von Behring* regards it as possible to feed nurslings with milk of cows made immune against tuberculosis and thus to convey to them antibodies which may serve to protect them from infection.

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§ 171. **Tuberculosis** is at the beginning a **local disease,** which occurs most frequently in the lungs, intestinal tract, and skin; that is, in places accessible from without. *Cases of cryptogenic infection* are by no means rare; in these the first demonstrable changes appear in tissues concealed in the deeper portions of the body-parenchyma — for example, in the lymph-nodes, adrenals, bones, joints, brain, tubes — and it is to be assumed that under certain conditions the bacilli enter the body without causing detectable changes at the point of entrance, and develop in some distant organ to which they are carried by the blood or lymph, and through multiplication give rise to tissue-degeneration, emigration of white blood-cells, and proliferation of tissue.

The **local disease** usually begins with the formation of **miliary tubercles** — that is, cellular nodules of the kind described above — which arise in the tissue singly or (in case of multiple infection) in great numbers simultaneously, or one after another (secondary dissemination of the multiplying bacteria). The tissue in the neighborhood of the individual tubercles, as well as that between the tubercles, shows more or less pronounced inflammatory exudation and proliferation of a cellular type; through these processes there are frequently formed **large granulation-areas** in the infected connective tissue.

In *surface colonization of the bacilli,* such as is possible in the alveoli of the lung and in the smallest bronchioles, **exudative catarrhal inflammation** may be the first sign of the infection, while proliferative processes in the çonnective-tissue stroma and in the pulmonary vessels appear at a later period.

In mucous membranes and in the skin (Fig. 428) large areas of mucosa and submucosa, or corium respectively, may undergo, through the formation of such granulations, nodular or diffuse flattened thickening. In serous membranes there may develop large, flattened nodules in whose neighborhood the serosa is thickened and covered with fibrinous exudate. In the synovial membrane of joints and bursæ there often arise soft, spongy proliferations, the so-called *fungous granulations* (Fig. 429); in the periosteum and bone-marrow round, grayish-red, or gray granulation-areas of varying size appear. All these areas have one feature in common — namely, in their neighborhood are found inflammatory infiltrations and proliferations of tissue, which bear the character of **granulation tissue** (Figs. 428, *a;* 429, *b*) inclosing char-

FIG. 429.—Tuberculous granulation tissue from the synovial membrane of the knee-joint (Müller's fluid, Bismarck brown). *a,* Connective tissue; *b,* granulation tissue; *c,* tubercle. × 80.

acteristic non-vascular, cellular nodules — **tubercles** (Figs. 428, *d;* 429, *c*)— which often contain giant-cells. In grayish-red tissues rich in blood the tubercles may often be recognized by the naked eye as gray, or, when undergoing caseation, as white or yellowish-white nodules.

The *area of tuberculous granulation tissue* becomes larger by *appositional growth,* by means of which the same processes, as just described, consummate themselves at the periphery. There may arise in this way, either in an infected organ, or on its surface, nodules of large size, **solitary tubercles** (Fig. 430, *c*) for example, in the pia, brain, and on the dura

mater, that not infrequently resemble tumors. Further, the tissue transformed by the tuberculous process or the newly formed tissue respectively, may suffer various fates; there may be distinguished three chief forms of termination, w h i c h may, however, be combined in various ways.

In one group of cases the production of connective tissue results in induration (Fig. 431) with the development of dense, fibrous tissue (*a*). If the process does not come to a standstill, there may be found in association with the fibrous tissue *proliferations of granulation tissue* (*b*), and often a larger or smaller number of typical *tubercles* (*c*). If the process comes to a **standstill** and to **cure of the infection,** the entire area may be converted into dense fibrous tissue (Fig. 432, *a, b*) which in part shows a nodular arrangement (*a*), and in part is hyaline and homogeneous in character. In the lungs such connective-tissue nodules contain more or less carbon-pigment (Fig. 432).

FIG. 430.—Large solitary tubercle of the pia mater of the cerebellum in vertical section. *a*, Cerebellum; *b*, dura mater adherent to the tubercle; *c*, laminated tubercle; *d*, gray peripheral zone adherent to the dura mater and beset with yellowish-white, nodular deposits. Natural size.
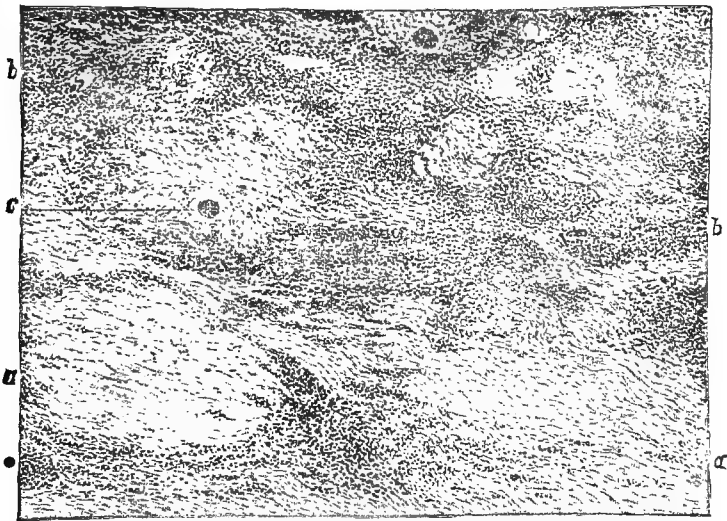
FIG. 431.—Tuberculous induration of the lung (alcohol, hæmatoxylin, and eosin). *a*, Dense, fibrous tissue; *b*, cellular granulation tissue; *c*, giant-cells. × 40.

A second form of termination is a **combination** of **caseation** and **fibrous induration** comprising dense fibrous tissue (Fig. 433, *b, d*) and caseous foci (*a*) of varying size.

The third termination consists essentially in **caseation,** the tuberculous granulation tissue dying and producing no connective tissue at all, or only in such slight amount that it is completely overshadowed by the caseous masses (Fig. 434, c).

Both the fibrocaseous and the purely caseous areas may become healed, through *encapsulation by the surrounding* connective tissue (Figs. 433, b; 434, c, e). Such healing can be regarded as complete only when in the connective-tissue capsule (Fig. 434, c, e), and its neighborhood (a) neither fresh granulation-tissue nor tubercles are present. Occasionally **calcification** of the encapsulated caseous mass may occur as a further sign of termination of the process.

The **caseous masses** of tuberculous foci are sometimes firm, sometimes soft, and in the latter case often suffer **disintegration** and **lique-**

Fig. 432.—Tuberculous induration of the lung (alcohol, hæmatoxylin, eosin). *a.* Homogenous fibrous nodules poor in cells and in part pigmented; *b,* diffuse induration of the lung. × 24.

faction leading to the formation of milk-white, crumbling, and pultaceous or thin fluid masses, so that the tuberculous area presents the picture of an **abscess** (*cold abscess*). Rupture and emptying of the abscess externally leads to the formation of **cavities** and **fistulous passages** and to **ulcers.**

Disintegration and cavity-formation occur particularly in the lung, and may lead to cavities as large as a man's fist or larger. They also occur not infrequently in caseating lymph-nodes, and in caseous foci in the kidneys, brain, muscles, skin, and bones (Fig. 435). The cavities (h) contain in the beginning the liquefied tuberculous tissue, in which remains of the original tissue may not infrequently be recognized in the form of sequestra (f). After evacuation of the contents the wall may furnish sufficient material to fill the cavity again, through secretion of pus or the breaking-off of necrotic tissue. *Hæmorrhages* commonly arise through erosion of blood-vessels.

The walls of the caverns and abscesses are lined by caseating granulation tissue containing tubercles (Fig. 435, *e*); the surrounding tissue becomes indurated, and the seat of caseating foci.

Ulcers occur most frequently in mucous membranes (Fig. 436, *h*) and in the skin, since the softening caseous masses in these regions most frequently break through to the surface. The edges and base of the ulcers are surrounded by a zone of infiltrated granulation tissue, often containing tubercles.

If a tuberculous focus does not become healed through induration, sequestration or encapsulation of the dead tissue, or through the removal or death of the bacilli, there exists the **danger of metastasis.**

This takes place oftenest by the lymph-channels; and a part of the
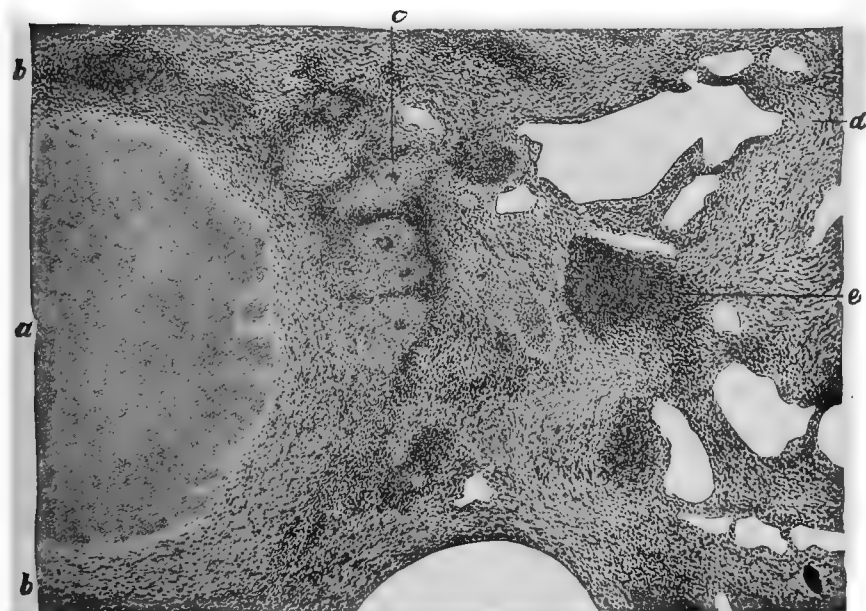
FIG. 433.—Encapsulated area of caseation of the lung with induration and eruption of tubercles in the neirhborhood (formalin, alcohol, hæmatoxylin, eosin). *a*, Caseous area; *b*, fibrous capsule; *c*, tubercle; *d*, indurated lung tissue; *e*, area of granulation tissue. × 40.

picture of progressive tuberculosis is the development of tubercles in the lymph-spaces and in the walls of the lymph-vessels (Figs. 436, *i*, *i₁*; 437, *e*, *f*, *g*, *h*, *i*) in the neighborhood of the primary focus.

Lymphogenous miliary tuberculosis is in some cases limited to the immediate neighborhood of the primary focus (Fig. 437), at other times it involves larger areas and may, for example, extend from a caseating tubercle in the lung over a large part of the pulmonary lymphatic system. These lymphangoitic tubercles present the appearance of gray nodules, often surrounded by a red zone, and consist essentially of the same structure as the primary focus.

The *lymph-nodes* may be affected early and tubercles develop in them, leading through successive crops to more or less enlargement and finally to caseation of the nodes, or to induration, or to a combination of these

31

processes. The *thoracic duct* may become infected from caseating and disintegrating lymph-nodes, and through this channel infection of the blood may take place.

Often the **formation of metastases takes place through the blood-stream**; in the first place, by the entrance of bacilli through the lymph from the thoracic duct as mentioned above, but also as the result of *direct entrance into the circulating blood.* In tuberculous tissue bacilli may pass directly into small veins, though obstruction to the circulation due to closure of the vessels usually prevents further dissemination. Often enough the bacilli gain entrance into larger veins — for example, through adhesion of caseating lymph-nodes at the hilum of the lungs with neighboring veins, the tuberculous process thus involving the vein-
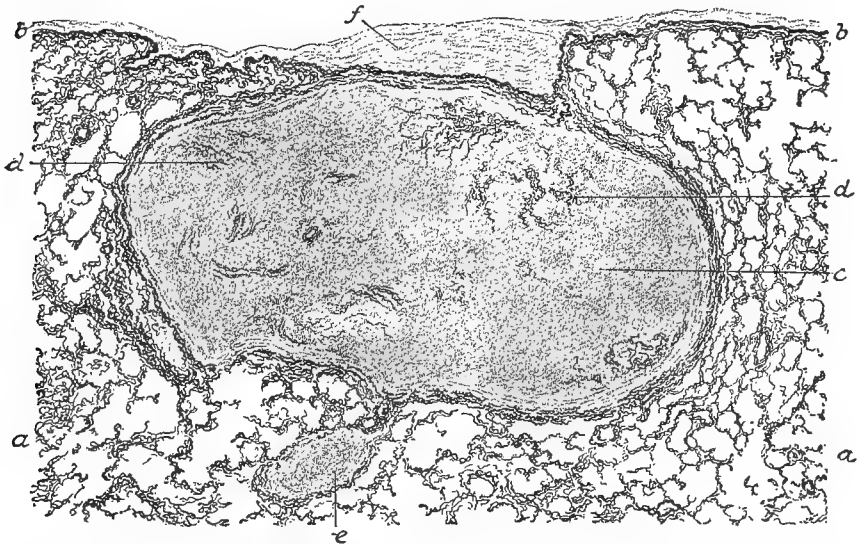
FIG. 434.—Encapsulated area of tuberculous caseation in the lung. *a*, Normal lung tissue; *b*, pleura; *c*, area of caseation; *d*, remains of elastic fibres in the area of caseation; *e*, small encapsulated caseous nodules; *f*, thickened pleura. × 15.

walls by direct extension. Moreover, *infection of veins* may occur in the neighborhood of a tuberculous focus, so that the small veins of an entire vascular system may present well-marked tuberculous disease — that is, inflammatory proliferation of the vessel-walls with the formation of tubercles and subsequent caseation (Fig. 440, *b*), and, if thrombosis does not occur, large numbers of bacilli may enter the blood-stream from the diseased walls. In rare cases the arteries, particularly the pulmonary arteries, become tuberculous through infection from surrounding tissues, and may give off bacilli to the blood-stream.

The transportation of bacilli through the blood-stream gives rise to **hæmatogenous miliary tuberculosis** — that is, to an eruption of miliary tubercles (Fig. 441, *a*) at those places where the bacilli become lodged and multiply. Just where these places will be, and how numerous the tubercles, depend on the location of the point of rupture and on the number of bacilli entering the blood. The entrance of many bacilli may lead to *general miliary tuberculosis.*

If bacilli enter the blood-stream in small numbers and are deposited in only one organ, and if death does not ensue, there arises in this organ progressive *local tuberculosis*.

The **exudative inflammation accompanying lymphogenous and hæmatogenous eruption of tubercles** is sometimes more, sometimes less pronounced, and is usually most severe in the meninges and in the lungs.

Should a tuberculous focus in the lung break into a bronchus, as the result of softening of a caseous area, or if a caseating focus in the kidney should invade the kidney-pelvis, there will result **dissemination of tuber-cle-bacilli over the surface of the mucous membranes.** From the bronchi the bacilli spread into the trachea, larynx, mouth-cavity, and
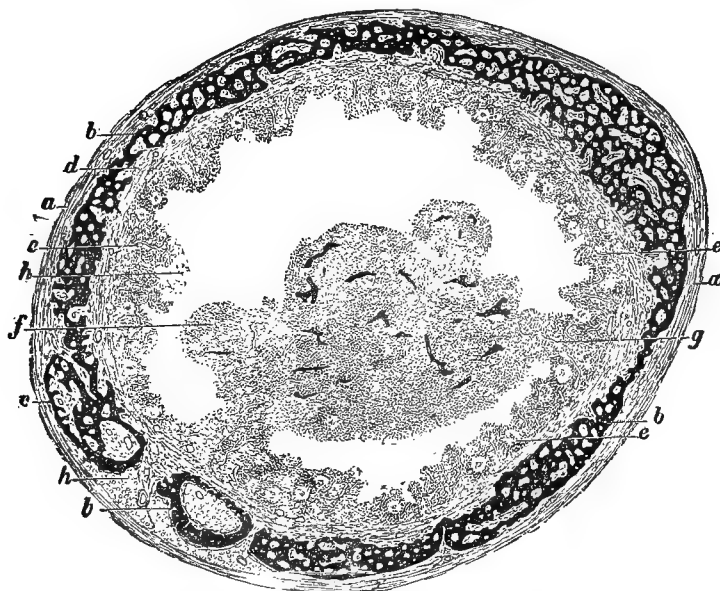
FIG. 435.—Tuberculous cavern in the tibia (alcohol, picric acid, hæmatoxylin, carmine). Transverse section. *a,* Periosteum; *b,* rarefied cortex; *c,* periosteal deposit of bone; *d,* fibrous tissue on the inner surface of the cortex; *e,* granulation tissue containing tubercles; *f,* sequestrum with bony trabeculæ, infiltrated with granulation tissue; *g,* union of the granulation tissue with the sequestrum; *h,* cavity that had been filled with pus and caseous masses. × 3½.

thence into the alimentary canal; through aspiration they may be carried into other portions of the lungs. From the kidneys the bacilli may spread through the descending urinary passages.

Secondary infection may result from this spreading of the bacilli, although only a small percentage thus distributed give rise to infection; experience has taught us that only certain portions of the mucous membranes are susceptible to infection — notably the tonsils and the lymphade-noid tissue of the intestines, while the œsophagus and stomach are almost immune; in the descending urinary passages, the kidney-pelvis, the ureters, and bladder are usually infected, while the urethra almost always escapes.

If **bacilli enter the great body-cavities** they may spread over the surfaces of the serous membranes, infect the latter, excite diffuse inflammation and the formation of nodules (Fig. 442). New-formations of connective tissue may follow later

Should tubercle-bacilli be present in the circulating blood of a woman during pregnancy, **infection of the placenta and fœtus** may follow, so that the child will be born infected. In so far as data concerning this point exist, this event is not of frequent occurrence; it is more usual for *children of tuberculous parents to become infected after birth.* Conceptional infection of the embryo through infected semen has not been demonstrated, and is unlikely.

Secondary infections are not infrequently associated with that caused by tubercle-bacilli; this occurs particularly when tuberculous cavities or ulcers are accessible from without. *Secondary infections of tuberculous lungs* are of frequent occurrence, and are due particularly to *streptococci* and *staphylococci, pneumococci, influenza-bacilli, micrococcus tetragenus,* and *baterium coli.* Many authors are inclined to refer all severe inflam-
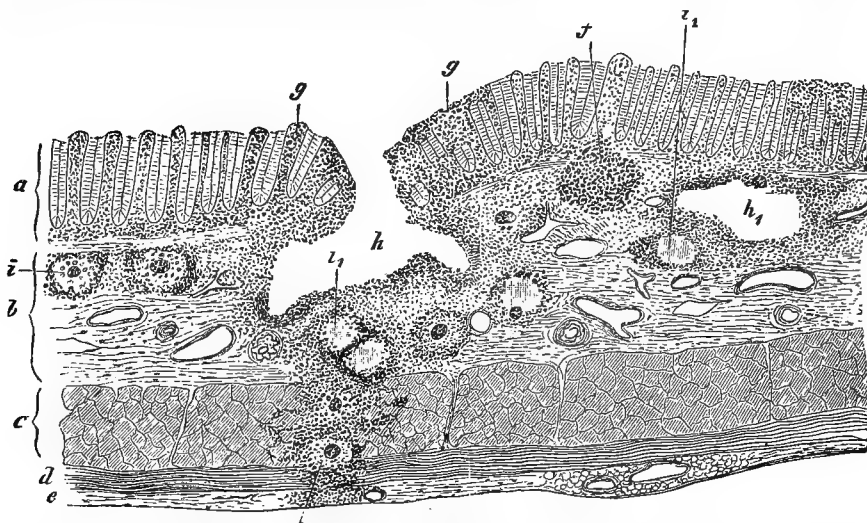
Fig. 436.—Tuberculous ulcer of the intestine with eruption of tubercles in the neighborhood (alcohol, Bismarck brown). *a*, Mucosa; *b*, submucosa; *c*, muscularis interna; *d*, muscularis externa; *e*, serosa; *f*, solitary follicle; *g*, mucosa infiltrated with cells; *h*, ulcer; *h₁*, area of softening; *i*, recent, *i₁*, caseous tubercle. × 30.

matory exudations accompanying pulmonary tuberculosis to secondary infections; but this is not correct in that the formation of tubercles by tubercle-bacilli may be accompanied by inflammatory exudations of such severity that serous or serofibrinous, or pure fibrinous, or fibrinopurulent exudates may collect in large quantities in the tissues (in the pulmonary alveoli, on the pleura, and in the subarachnoid space, etc.). High (septic) fever, rapid destruction of tissues with a tendency to suppuration, and unusually severe inflammation, in part of hæmorrhagic character, point to secondary infection. Nevertheless, it is often impossible to determine, without special investigation directed to this point, whether pure tuberculosis or mixed infection is present.

For the treatment of tuberculosis with bacterial extracts and curative serum see § 32.

The question as to how often **tuberculosis is transmitted by the passage of bacilli from the mother to the child** is an open one. It has, however, been shown by *Schmorl, Birch-Hirschfeld,* and *Landouzy* that in cases of miliary tuber-

culosis in pregnant women, tubercle-bacilli are present both in the intervillous spaces and in the blood of the chorionic vessels, and that the liver of the fœtus may contain bacilli. Further, cases of tuberculosis of the placenta occur (*Schmorl, Kockel, Lungwitz, Warthin* and *Cowie*), which may be regarded as stages on the way of the tubercle-bacillus from the mother to the fœtus.

Cases of tuberculosis occurring at an early period of life reported by *Demme, Baumgarten, Rilliet, Charrin,* and others, as well as the statements of *Armanni, Landouzy,* and *Martin,* that the inoculation of portions of the organs of human fœtuses obtained from tuberculous mothers produced tuberculosis in guinea-pigs, speak in favor of passage of tubercle-bacilli from the mother to the fœtus. Still more important are the experimental investigations of *de Renzi* and *Gärtner,* who succeeded through the inoculation of pregnant guinea-pigs, white mice, and rabbits in producing tuberculosis in a part of the young born of these animals. *Gärtner*
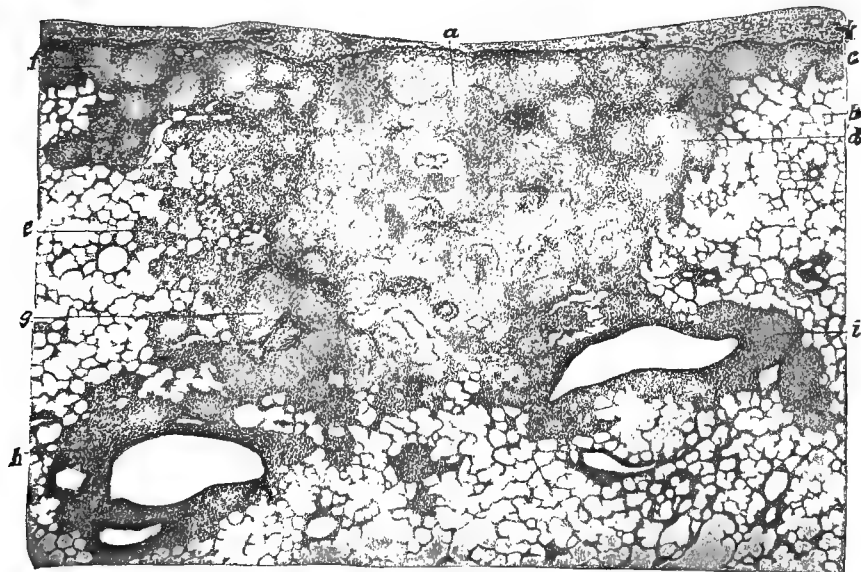
Fig. 437.—Beginning tuberculosis of the lung without catarrh (alcohol, orcein). *a,* Caseous area with remains of elastic tissue; *b,* normal lung tissue; *c,* pleura with tubercles; *d, e,* tubercles in the neighborhood of the caseous area; *f,* tubercle in the pleura; *g,* periarterial, *h,* peribronchial, *i,* perivenous tubercles of the lymph-vessels; *k,* new-formation of fibrous tissue beneath the limiting elastic layer of the pleura. × 16.

is consequently of the opinion that under certain conditions tubercle-bacilli may pass from the mother to the fœtus in the case of both animals and man. Finally, *Maffucci* and *Baumgarten* succeeded in effecting transfer of tubercle-bacilli to impregnated hen's eggs, and discovered that the infection did not disturb the development of the chick, but, on the contrary, the bacilli that were taken up by the embryo remained in the tissue of the latter without multiplying to any extent, later to cause tuberculosis in the body of the hatched-out chick. According to the evidence of anatomical investigations *placental transmission of tuberculosis to the child cannot be doubted.* On the other hand, conceptional transmission of tuberculosis from the father to the embryo has not been proved. Moreover, according to the investigations made up to the present time it may be emphasized that *tuberculosis is to be referred usually to extrauterine infection* and that *children of tuberculous parents* suffer from tuberculosis so frequently because they are *more exposed to infection* than are the children of healthy parents. Special *predisposition to tuberculosis in the children of tuberculous parents* has not been demonstrated.

In animals transmission of tuberculosis to the fœtus seems occasionally to occur, according to the reports of *Zippelius, Jessen, Pütz, Grothans, Malvoz, Lydtin, Brouvier, Adams,* and others. *Johne* was not only able to demonstrate in a fœtal calf the presence of miliary nodes and larger nodules in the lungs, liver, and various lymph-nodes, but to show the presence of characteristic bacilli in the lesions.

By clinicians so-called **scrofula** is often regarded as a special pathological condition of the organism of the child, predisposing it to tuberculosis. As scrofulous are regarded those children who frequently suffer from inflammations of the mucous membranes (nose and its accessory cavities, conjunctiva, middle ear), as well as of the skin, from swelling of the lymph-nodes, leading occasionally to necrosis and suppuration, finally from chronic inflammations of the bones and joints, and who present a flabby, pale, often bloated appearance. In many cases these symptoms are due to tuberculosis; in other cases they are caused by infection with streptococci or staphylococci, or are the results of syphilis. Scrofula is not a disease-entity, but a special symptom-complex belonging to different diseases. Whether the affected children possess *special predisposition to all these infections* which may be designated *scrofula* is difficult of proof. The organism of the child is in general easily infected by these agents, and the frequent illness of certain children due to these infections

Fig. 438.—(Bellevue Hospital.) Tuberculosis of lymph-nodes of neck.

may be referred to lack of cleanliness, or to conditions of environment, or to injuries, etc., as well as to predisposition of the child itself. According to the elder *Gross,* many so-called scrofulous children are born with the stigmata of status lymphaticus and are hence more susceptible to infections, particularly those that enter through the lymphoid tissues.

Von Behring upheld the view that tuberculosis is almost always the result of bacilli entering through the intestine in infancy, and that later infections play a subordinate rôle. This theory is correct in so far as the long-known fact is concerned, that the intestine of infants takes up bacilli more easily than the adult intestine, and that infection is not always manifest at the point through which the bacillus enters, but develops in those organs, the lymph-nodes, lungs, brain, bones, etc., to which it has been carried by the blood or lymph. Infection with tubercle-bacilli may occur at any age. The primary intestinal infection is not the dominating one, but the infec-

Fig. 439.—Eruption of tubercles in a lymph-gland (alcohol, hæmatoxylin). *a,* Tubercle; *a₁,* caseous tubercle; *b,* tissue of the lymph-gland; *c,* giant-cell in the centre of a tubercle; *c₁,* giant-cell at the edge of a caseous focus; *d,* large-cell tissue between the tubercles; *e,* blood-vessel. × 150.

tion of the respiratory tract is. The latter usually results from direct entrance of the bacilli into the respiratory parenchyma. Primary infection of the nose, larynx, trachea, and bronchi also occurs, but is relatively less frequent than primary lung-infection.

Calmette's view of the intestinal origin of anthracosis has also been turned as an argument favoring the ingestion-theory of tuberculosis. Much has been written on this subject during the last several years, and while the opinion of the majority of pathologists favors the aërogenous nature of tuberculous infection in late childhood and adult life, the etiological importance of infection through the intestine in infancy cannot be disregarded.

Tuberculosis of mammals is observed most frequently in *cattle*, and presents a course similar to that of the disease in man, though the granulation-areas develop more frequently into tumor-like nodules, particularly in cattle, and the tendency to generalization of the disease is less. The tuberculosis of serous membranes which is often designated **pearl disease** begins with the
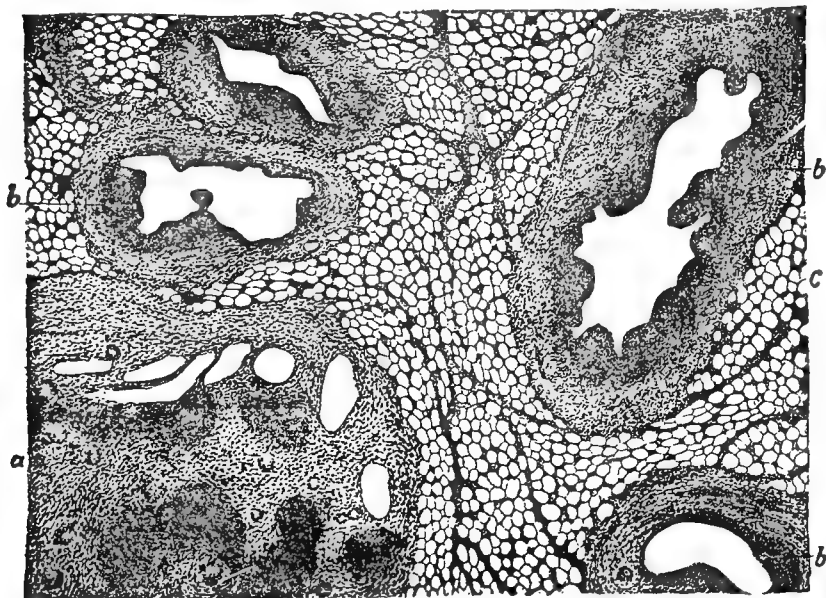
Fig. 440.—Tuberculosis of the veins in the neighborhood of a tuberculous retroperitoneal lymph-gland (formalin, hæmatoxylin, eosin). *a,* Tuberculous lymph-gland with giant-cells and caseous foci; large blood-vessels at the periphery; *b,* veins whose walls are thickened by tuberculous granulation tissue, the inner layers of which show caseation; *c,* fat tissue. × 28.

formation of small nodules, leading then to more marked proliferation of connective tissue, giving rise to the formation in the thickened serosa of nodules the size of a pea or bean or even as large as a hen's egg or man's fist, which in the beginning are soft and sarcoma-like, but later become firm and dense and often enclose calcified areas. The form of the proliferation is sometimes villous-like and warty, at other times mulberry- or grape-like, cauliflower-like or polypoid.

Next to cattle the *hog* is most frequently affected with tuberculosis, more rarely the horse, goat, sheep and cat, and still more rarely the dog.

Of *wild animals* in captivity, the ape, lion, tiger, bear, jackal, panther, jaguar, giraffe, and dromedary easily acquire tuberculosis. Of the small animals used for experiment the guinea-pig is the most susceptible. After subcutaneous inoculations there results progressive tuberculosis which kills the animal in from about four to eleven weeks. In rabbits inoculation tuberculosis may heal. Field mice and white mice are infected with difficulty.

Tuberculosis is of frequent occurrence in **birds** (chickens, pigeons, pheasants, and parrots), and is usually localized in the abdominal organs.

The cultures of tubercle-bacilli from man are dry, warty, or scaly and lustreless; those of avian tuberculosis moist, wrinkled, and soft, and grow best at 43° C.

Dogs are immune to avian tuberculosis, but not to human tuberculosis. The intra-peritoneal inoculation of m a m m a l i a n tuberculosis (*Leray*) causes in rabbits numerous caseous foci in the liver and spleen with few giant-cells and scanty bacilli, and in the lungs caseous nodules containing numerous bacilli. Inoculations into these animals of chicken-tuberculosis, on the other hand, cause scanty production of non-caseating cellular proliferations containing giant-cells and great numbers of bacilli.

According to *Maffucci, Martin, Gärtner,* and others, the inoculation of human tuberculosis into chickens does not produce tuberculosis, although the bacilli remain alive for weeks in the body of the chicken. Pigeons (*Auclair*) die after intra-peritoneal inoculation, but no tubercles are found in the tissues; the liver and lungs may contain living bacilli fourteen days after inoculation. In guinea-pigs (*Straus*) the bacilli of human tuberculosis cause more severe changes than do the bacilli of chicken-tuberculosis.

FIG. 441.—Hæmatogenous miliary tuberculosis of the liver (alcohol, carmine). *a,* Developed tubercle in the connective tissue about the portal vein; *b,* collection of leucocytes. × 150.

In mice infected with avian tuberculosis (*Weber* and *Bofinger*) there occurs moderate increase of the bacilli without intoxication and without marked reaction on the part of the tissue. When kept in the mammalian body (guinea-pigs and mice) for one or two years the virulence of avian bacilli for guinea-pigs is not changed. Whether man is susceptible to avian tuberculosis is still an open question.

The **question whether tuberculosis of animals, particularly of domestic animals, is identical with that of man** has been the subject of lively discussion. The majority of writers believe in their identity. *Koch* and *von Baumgarten* deny it. In favor of the latter view may be taken the fact that the bacilli of different sources show differences in cultures, cultures of avian tuberculosis in particular showing essential differences from those of human tuberculosis. Further, inoculations of human tubercle-bacilli into domestic animals, for example, cattle, are either negative or cause a milder disease than that resulting from the in-

FIG. 442.—Tuberculosis omenti (Müller's fluid, carmine). *a,* Centre of tubercle; *b,* cells of epitheloid character; *c,* lymphatic elements; *d,* proliferating epithelium (endothelium) in the neighborhood. × 200.

oculation of bacilli obtained from sick cattle. In spite of these facts it cannot be doubted that we have to deal, not with different forms of disease, but that the tuberculosis of man and that of the domestic animals are identical

diseases produced by **varieties of the same species of bacillus.** When the bacilli increase for a long time in the same species of animal they acquire properties that make them less virulent for other species and they are with difficulty made to grow in the latter. Human tuberculosis is nevertheless still directly transmissible into other mammals, and man may be infected with the bacilli of mammalian tuberculosis. Uncooked cow's milk and meat containing tubercle-bacilli can convey bovine tuberculosis into man, and the attendants of cattle can be infected from sick animals through wounds or the respiratory tract. The avian strain of tubercle-bacilli is the farthest removed in its properties from the human strain. In parrots there occurs tuberculosis the bacilli of which are identical in their properties with those of human tuberculosis.

Tuberculosis occurs also in cold-blooded animals, fish, blind worms, frogs, snakes, lizards, tortoises, etc., and is likewise caused by an acid-fast bacillus, that possesses an optimum of growth at 15° C., and grows at temperatures of 10°–31° C. It has been assumed (*Bataillon, Ferre,* and others) that this bacillus is a variety of the bacillus of mammalian tuberculosis. *Friedman* attempted to immunize guinea-pigs against tuberculosis by inoculating them with less virulent bacilli of the tuberculosis of cold-blooded animals.

As **pseudotuberculosis** may be classed those affections characterized by the formation of cellular and fibrous nodules, in part undergoing necrosis, and which are similar to tubercles, but which are not caused by *Koch's* bacillus. According to etiology the following forms may be distinguished:

1. *Pseudotuberculosis due to dead foreign bodies.* This may be caused by the experimental injection of lycopodium-spores, olive-oil, and mercury into the blood-vessels, the inhalation of irritating material into the lungs, the injection of large quantities of milk into the peritoneal cavity, etc. The presence in the tissue of caterpillar hairs, pieces of wadding, silk threads, cholesterin tablets from ruptured ovarian cysts, etc., may lead to the formation of fibrocellular nodules.

2. *Pseudotuberculosis caused by monomorphous* and *polymorphous bacteria.* *Eppinger, Bucholz,* and *Flexner* have described forms of *Cladothrix* and *Streptothrix* obtained from apparently tuberculous lungs and bronchial glands which they are inclined to regard as the cause of the disease. *Courmont* found in an apparently tuberculous elbow-joint a bacillus which was not identical with *Koch's* bacillus. An affection of the peritoneum resembling tuberculosis may be produced in guinea-pigs by injection of the butter-bacillus of *Rabinowitsch* (which probably comes from cow-dung) as well as by the grass-bacillus of Moëller; and in white mice by inoculation of the butter-bacillus of *Korn.*

In rodents a disease resembling tuberculosis is not infrequently produced by a plump, thick bacillus with rounded ends (*Pfeiffer, Preisz, Zagari, Nocard, Bonome, Delbanco,* and others). Other forms of bacillary pseudotuberculosis have been observed in rabbits (*Eberth*), in birds (*Muir*), in the cow (*Courmont*), etc.

3. *Pseudotuberculosis due to hyphomycetes* occurs in the lungs and may be produced artificially by the injection of different forms of aspergillus and mucor; but the affections so produced show peculiarities which permit differentiation from true tuberculosis.

4. *Pseudotuberculosis caused by animal parasites* occurs in the sheep, hog, goat, cat, hare, roe, stag, and chamois, and is caused by different forms of *Strongylus* and by *Pseudalius capillaris (Müller)*; it is a vermian pseudotuberculosis.

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§ 172. **Syphilis,** like tuberculosis, is an infectious disease, which, from a local infection, spreads throughout the body by the blood- and lymph-channels, and leads to the formation of localized inflammations and pro-liferations of granulation tissue, which, however, do not present so characteristic a structure as the tubercle.

In 1905 *Schaudinn* and *Hoffman* announced the discovery of the constant occurrence in syphilitic lesions of a characteristic organism. Control examinations of non-syphilitic lesions failed to reveal it. To the newly discovered parasite the name of **Spirochæte pallida** was given. Corroboration of the finding of *Schaudinn* and *Hoffman* was soon forthcoming from investigators in all parts of the world. It was found to be constantly present in the primary lesions, in all forms of secondary and tertiary lesions, in the blood, lymph, and cerebrospinal fluid of syphilitics, in the lesions of congenital syphilis and in the blood, lymph, cerebro-spinal fluid and organs of cases of congenital syphilis, and in the placenta of such cases. It has also been demonstrated in the experimental syphilis of apes (*Met-schnikoff* and *Roux,* Ann. de l'inst. Pasteur, 1903, 1904, 1905). The spirochaete of syphilis has recently been cultivated on artificial media and its etiological signifi-cance is now established beyond all doubt (*Schereschewsky, Mühlens, Nogouchi, Zinsser* and *Hopkins*).

The *Spirochæte pallida* is a delicate, non-refractile spiral organism, varying in length from 2–20 μ, the average length being about 4–14 μ. The spirals are tight and corkscrewlike, fading out at the pointed ends. They vary in number from three to twenty-five or more. The large number of spirals in proportion to the length of the entire organism is characteristic. The whole organism is usually somewhat curved. Delicate terminal flagella have been observed. The spiral form is retained when the organism is at rest. It has the power of rotation on its long axis, of moving forward and backward, and of making whip-like undulations. A nucleus has not been demonstrated. It does not bear spores and no evidence of transverse division has been observed. *Schaudinn* believed that it possesses an undulating membrane. At the present time it is not definitely decided whether to regard the organism as a protozoon or as a spirillum. *Schaudinn* favored the former view. In accordance with this belief the names *Spironema* and *Treponema pallidum* have been proposed for it.

The *Spirochæte pallida* stains poorly, but can be demonstrated in smears from primary lesions by Wright's stain, the Romanowsky or Giemsa stain. It is import-ant that the smears be stained as soon as made; it often cannot be found in smears that are not perfectly fresh. From the *Spirochæte refringens* it is distinguished by its delicacy, pale staining, and the number of its spirals and their tight, cork-screw arrangement. The refringens is larger, thicker, more refractile, stains easily, and has broad, wavy spirals, and its ends are usually blunt. Levaditi's method may be used for staining the pallida in sections. The micro-organism in the living state may be demonstrated by appropriate methods (hanging-drop preparation and dark-field illumination) and is an easy and extremely valuable means of early diagnosis.

The infective agent through whose inoculation syphilis is produced occurs only in the human organism, where it is reproduced, and com-municated by direct or indirect transfer. Metschnikoff, Roux, Lassar, and Neisser succeeded in conveying syphilis to anthropoid apes (the chimpanzee) through the inoculation of syphilitic tissue. When im-planted the infective agent excites inflammatory processes of varied in-tensity and extent — from local transitory hyperæmia to the production of large tumor-like granulations, or extensive hyperplasias of connective tissue. The child of a mother infected with syphilis may receive infection through the placenta.

In acquired syphilis the first focus of inflammation develops at the point of infection, which is usually located in the skin or mucous membranes (mouth, throat, mucosa of genital apparatus). There is first formed a papule which spreads towards the surface, and within eight
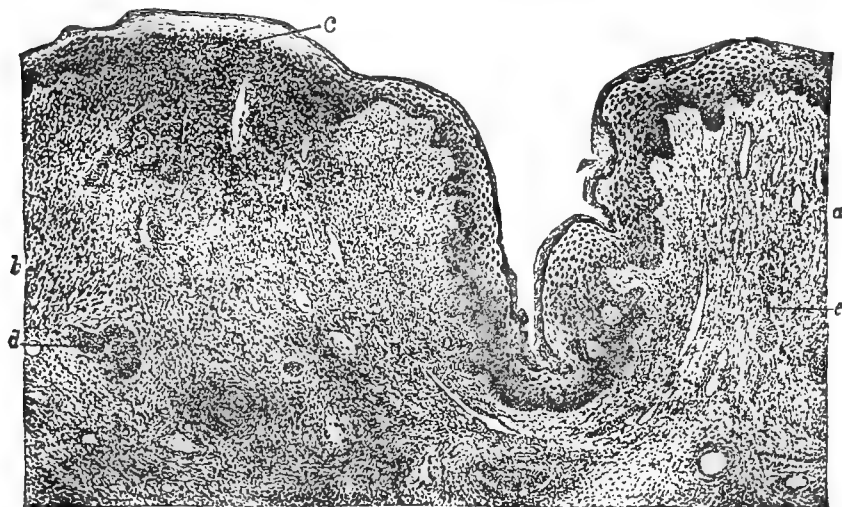
FIG. 443.—Initial sclerosis (alcohol, hæmatoxylin, eosin). *a*, Corium, slightly inflamed; *b*, initial sclerosis; connective tissue infiltrated with cells; *c*, rupture of the cells into the epithelium; *d*, *e*, lymph-vessels filled with round cells. × 35.

to ten days forms scales, or ulcerates and secretes a small amount of serous fluid which dries to a scab; at the same time its base becomes hardened and forms a thick disc-like or a thin parchment-like deposit. Occasionally a vesicle is formed, this becomes an erosion, and then an ulcer with scanty secretion and indurated base. In still other cases an ulcer is first formed, and the base becomes indurated subsequently.

The induration is called the **initial sclerosis** (Fig. 443, *b*); the ulcer is known as a *hard chancre*. (Hunterian chancre). The former is caused by a collection of small *round cells* (Figs. 443, *b; 444, a*) in the spaces of the connective tissue. Occasionally *epithelioid cells* (Fig. 444, *b*) and *isolated giant-cells* are formed (*c*). With these changes the height of the process is reached; the tissue disintegrates and ulcerates, or is absorbed after disintegration.

FIG. 444.—Section from a syphilitic initial sclerosis (alcohol, alum carmine). *a*, Round-cell infiltration; *b*, large mononuclear formative cells; *c*, multinuclear giant cells. × 350.

A part of the cells is utilized in the formation of scar tissue.

Within the area of initial sclerosis and in its immediate neighborhood the lymph-vessels (Fig. 443, *d*, *e*) are dilated and filled with round cells. After the lapse of a certain length of time the lymph-nodes, skin, and mucous membranes become involved in inflammatory processes (symp-

toms of the secondary stage). Still later, there follow syphilitic inflam-
mations of the internal organs and the bones (tertiary stage). These,
in many respects, resemble non-syphilitic inflammations, but special
forms of granulation tissue are sometimes produced. The syphilitic
affections of the skin, which are grouped under the term **syphilides,**
sometimes form red spots, sometimes larger or smaller papillary
elevations which may be associated with vesicles and pustules as well

FIG. 445.—(Bellevue Hospital.) Ulcerative annular syphilide of back.

as with scales. Accordingly, the cutaneous syphilides are called by
different names, as follow: *Roseola syphilitica,* and *papular, macular,
papulo-macular, vesicular, pustular,* and *ulcerative syphilides* as well as
psoriasis syphilitica. A common element in these affections is inflamma-
tion, characterized by infiltration and in part by proliferation. Thus, in
the *large papular syphilide* or *condyloma latum* there is a teat-like eleva-
tion of the skin caused by infiltration of the papillary body (Fig. 446, *i*),
the corium (*k*), and the epithelium (*e, f, g, h*) with cells and fluid exudate
which coagulates, causing induration of the part. If the horny layer of
the epidermis becomes macerated, quantities of exudate appear on the
surface, and give rise to a moist condition of the condyloma. In pustular

syphilides inflammation leads to liquefaction of epithelium, and in the ulcerating forms to softening and disappearance of the papillary body and corium.

Inflammatory and degenerative changes appear in the secondary stage of syphilis, in the mucous membranes of the mouth, throat, and respiratory passages, particularly in the form of localized, whitish plaques known as mucous patches.

Syphilitic lesions of the tertiary stage in internal organs, glands, bones, muscles, subcutaneous and submucosal tissues, in the meninges of the
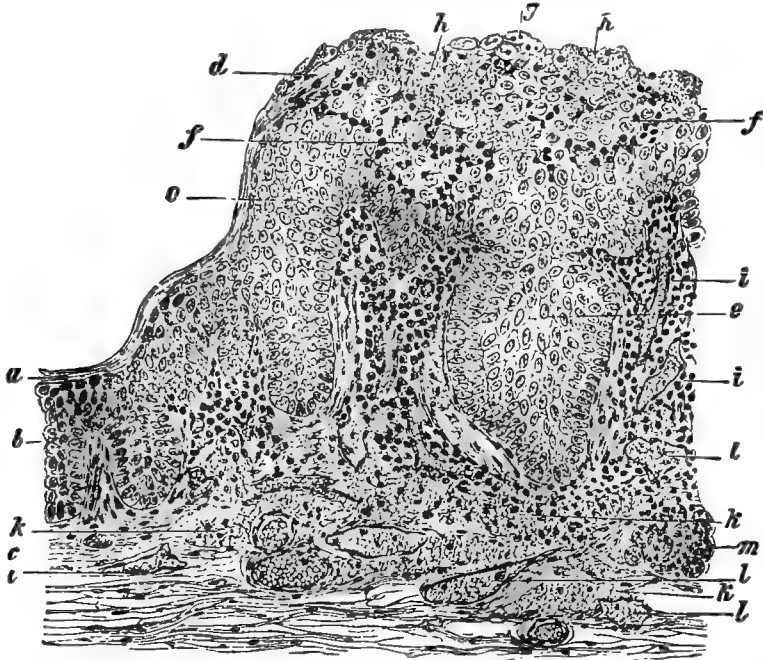
FIG. 446.—Condyloma latum ani (alcohol, Bismarck-brown). *a*, Horny layer; *b*, mucous layer of the epidermis; *c*, corium; *d*, loosened horny layer infiltrated with small cells; *e*, swollen, *f*, swollen and infiltrated mucous layer; *g*, epithelial cells containing round cells; *h*, granular masses of coagula; *i*, swollen papillary body infiltrated with cells and fluid; *k*, corium, swollen, and infiltrated with cells, fluid and coagulated albumin; *l*, dilated lymph-vessels filled with clots; *m*, sweat-glands. × 150.

brain, etc., consist of degenerative and inflammatory processes or hyperplasias of connective tissue without characteristic features, and are designated **gummata** or **syphilomata**. In its early stages the gumma represents a localized inflammatory process; it is usually rich in cells and undergoes central caseous necrosis (Fig. 447, d_2), while at the periphery, granulation tissue (d) and later connective tissue (d_1) are developed. The gumma occurs in the periosteum (Fig. 448) and membranes of the brain (Fig. 447), as well as in the parenchymatous organs, especially in the liver (Fig. 449, *a, b*), lymph-nodes and lungs.

In the meninges of the brain and spinal cord syphilitic inflammations lead to cicatricial thickenings and to the formation of gummata. Peri-

osteal syphilis occurs most frequently in the flat bones of the skull-cap, (Fig. 448), in the facial bones and the great long bones (tibia), but may extend over the greater part of the skeleton, and exhibits the character of a granulomatous inflammation which leads to scar-tissue and new bone, so that osteophytes or hyperostosis result. The severe forms, represented by gummata, lead to caries and necrosis. The fresh inflammatory focus appears as a translucent, yellow or grayish-white area surrounded by hyperæmic tissue that may extend to the marrow. The yellowish foci consisting of masses of small cells (Fig. 448, c) may die, the cells losing their nuclei (d); in such places necrosis of bone may
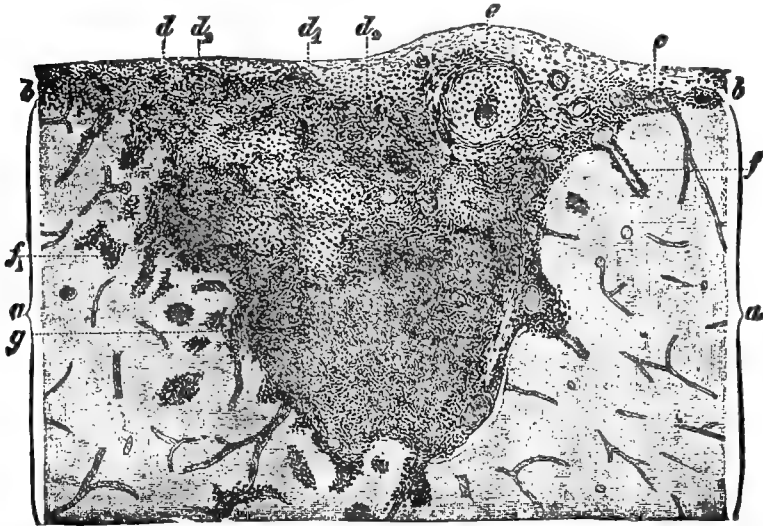
FIG. 447.—Meningo-encephalitis syphilitica gummosa (Müller's fluid, alcohol, hæmatoxylin). a, Brain cortex; b, inner meninges; c, vein surrounded by cellular exudate, d, fresh cellular granulation tissue; d_1, fibrocellular granulation tissue; d_2, caseated granulation tissue; e, artery with markedly thickened intima and adventitia infiltrated with cells; f, cellular infiltration of the pia-sheaths of the cortical vessels; f_1, perivascular cellular infiltration of the cortical substance; g, diffusely spreading cellular infiltration invading the brain-substance. × 14.

result. In living periosteal and endosteal tissue there occurs new-formation of connective tissue (e, f), which, with the formation of multinucleated osteoclasts (g) and of Howship's lacunæ, leads to destruction of the bony trabeculæ. In the process of healing this connective tissue may be changed into bone.

In the liver syphilitic lesions lead to the formation of radiating scars (Fig. 449, b, c, d), which often enclose cheesy remnants of the original inflammatory focus (a), that is, a gumma. The process is similar in other organs, for example, in the testicles and spleen.

The disintegration of syphilitic foci of the skin and subcutaneous tissue, and of the mucosa and submucosa, leads to the formation of ulcers, which, in mucous membranes, occur most frequently in the region of the mouth, throat, and upper respiratory tract. In the neighborhood of the ulcers in mucous membranes there are not infrequently papillary proliferations.

The cause of the disintegration and necrosis occurring in syphilitic inflammations lies in the peculiar character of the infective agent. A second factor is the extensive participation of blood-vessels, particularly arteries, in the inflammation. When syphilitic inflammation leads to the formation of granulation tissue or to connective-tissue hyperplasia, the vessel-walls become thickened, particularly the intima (Fig. 447, *e*) and the lumen is narrowed and not infrequently closed. Occasionally the syphilitic process is localized in the vessels.

Besides the foci of inflammation which point to localization of the spirochaete of syphilis, there not infrequently occurs in syphilitic individuals specific *degenerations of the central nervous system* (tabes, pro-

FIG. 448.—Syphilis of the skull-cap. *a*, Periosteum; *b*, bony trabeculæ; *c*, small-cell infiltration of the marrow; *d*, necrotic infiltrated marrow-tissue; *e*, periosteum proliferating into the bone; *f*, fibrous endosteum; *g*, osteoclasts and Howship's lacunæ. × 40.

gressive paralysis), associated with proliferation of neuroglia. Although these affections now regarded as *sequelæ of syphilis,* present no histological peculiarities characteristic of syphilis, they are universally accepted as due to infection by spirochaeta pallida. Spirochaetes have been demonstrated in the brains of subjects dead of general paralysis of the insane, or paresis. (Nogouchi and Moore.)

Hereditary syphilis is characterized by tissue-changes which differ from the manifestations of acquired syphilis, although changes occur which correspond to the latter. In the skin hereditary syphilis causes macular, papular, and pustular syphilides which may lead to ulceration. The liver, kidneys, adrenals, and bones may show circumscribed necrotic foci or cellular infiltrations. The spleen is usually more or less enlarged,

and may attain many times its normal volume. In the liver there occur collections of round cells in closely packed foci associated with new-formation of connective tissue in the perilobular spaces and with hyper-plasia of connective tissue throughout the liver (Fig. 452, *a*, *b*), giving to the organ a firm consistence and a peculiar yellowish-brown color (pericellular cirrhosis). The lungs may present, throughout or in part, a dense gray or grayish-white structure resembling that of sarcoma. This appearance is due to the formation of cellular connective tissue (Fig. 453, *a*, *b*) which contains imperfectly developed alveoli (*e*, *e*$_1$) and bronchi (*d*, *d*$_1$) or none at all. In cases of slight severity there is thicken-ing of the peribronchial and perivascular tissue and interalveolar septa,
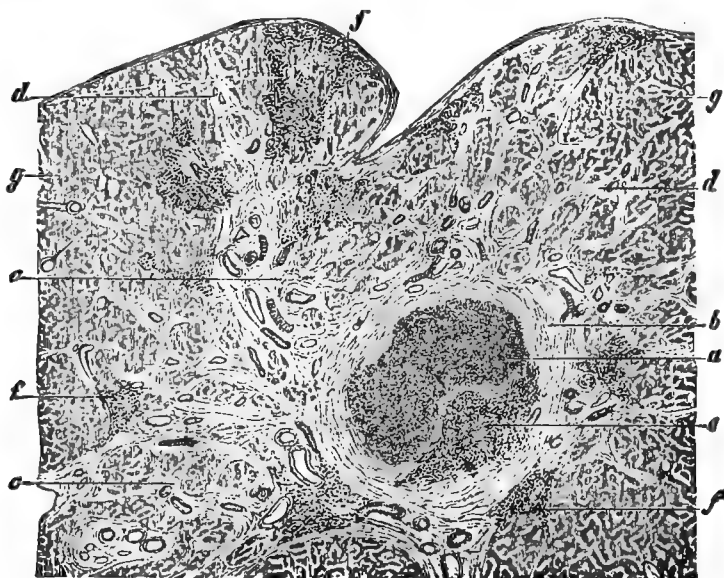
Fig. 449.—Gumma hepatis (alcohol, alum carmine). *a*, Caseous nodule: *b*, homogeneous connective tissue; *c*, connective tissue with remains of liver tissue; *d*, connective-tissue bands radiating into the liver tissue; *e*, cellular focus at the edge of the caseous nodule; *f*, cellular focus within the connective-tissue rays; *g*, liver tissue. × 12.

associated with accumulation of desquamated epithelium in the alveoli. Interstitial gummata may be present in the more advanced cases. The lesion is known as pneumonia alba (Virchow). In the kidneys and testi-cles the supporting connective tissue may be increased in places, and abnormally rich in cells. *Congenital syphilis often causes in glandular organs development of connective-tissue elements and collections of round cells,* while epithelial tissues are retarded. This is well shown in con-genital syphilitic pancreatitis, which is characterized by diffuse overgrowth of connective tissue and diminution in the glandular elements. Finally, there not infrequently occur in bones *disturbances* of *endochondral ossi-fication,* characterized by irregularity in the formation of the medullary cavity and by the deposit of lime-salts in the cartilage, leading to disturb-ances in the structure of the subchondral spongy bone-substance. Through the formation of granulation-tissue which undergoes caseous necrosis, larger defects may arise in the bone substance.

§ 173. The **Bacillus lepræ** (described by Armauer Hansen in 1879) is a slender bacillus, from 4 to 6 μ long. It is regarded as the **cause of leprosy.** It is found constantly in great numbers in the diseased tissues (Figs. 454, 455, 456) and in the excretions from leprous sores.

Foci of leprosy are characterized by proliferation (Fig. 454) of cells of different sizes and a fibrous ground tissue. The bacilli lie between (e), and in the cells (c, d), in the latter in such numbers that the cells become swollen (d) and changed into mono- and multinuclear giant-cells (Fig. 455). The latter occasionally enclose large vacuoles which contain great numbers of bacilli. The nuclei remain preserved for a long time, and are pressed to the periphery by the vacuoles containing the

Fig. 450.—(Bellevue Hospital.) Gumma of cheek.

bacilli. Later the nuclei are destroyed, and the cell becomes changed into a vacuole containing bacilli (Fig. 455).

The bacilli react to stains in much the same manner as tubercle-bacilli. The same methods may be used for the former as for the latter, with certain slight modifications, since the bacillus of leprosy stains more easily and is decolorized more readily than the tubercle bacillus. In tissues, the leprosy bacillus is easily to be detected by proper methods of staining, while the tubercle bacillus is evasive. The leprosy bacillus is less apt to display a beaded appearance and is rather less slender than the tubercle bacillus.

Attempts to cultivate lepra bacilli have led to no conclusive results. In the transplantation of leprous tissues into animals the bacilli do not multiply and leprosy is not reproduced.

The infection of man takes place by direst transfer from individual to individual. The nasal secretion is especially infectious when leprous lesions are present in the nose. In leprous affections of the respiratory

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tract the sputum contains bacilli; the excretions from ulcers in the skin contain them in vast numbers. Contagion seems to result most frequently from the nose; in favor of this view is the fact that the anterior nasal region is usually involved early. The bacilli are spread through the body by the lymphatic system; they may also invade the blood-stream.

The peripheral nerves are often concerned in the disease; the bacilli may also multiply in the testicles, liver, ganglia, and spleen, giving rise to foci of disease in these organs.

At the place of colonization the bacilli excite inflammation. Granulation tissue is formed; this for a long time is characterized by great richness in cells, and forms nodules and tumors in the skin and nose and spindle-shaped thickenings of the nerves. The tissue-proliferations often group themselves in the skin about the hair-follicles (Fig. 456, d), the ducts (f), and the coil (g) of the sweat-glands, although such a relationship is not always to be seen (h). Moreover, the bacilli may penetrate the hair-follicles, and sweat-glands, and thence the surface of the skin. Infection of the arterial walls causes arteritis, by which the walls become thickened and the lumina narrowed. In the nervous system the bacilli are found in the connective tissue and ganglion cells. The cells occupied by them undergo degeneration, with the formation of vacuoles.

Leprosy of the skin occurs oftenest on the face, on the extensor surface of the knees and elbows, and on the back of the hands and feet. It begins with the formation of red spots which vanish, leaving pigmented spots behind, or become elevated into nodules of a brownish-red color. In the region of the red spots the tissue contains large numbers of bacilli and even at this stage proliferation of cells can be demonstrated. According to Müller, the vesicular eruptions which occur in leprosy, and which were formerly regarded as sequelæ of leprous disease of the nerves, are caused by the presence of bacilli.

FIG. 451.—(Bellevue Hospital.) Syphilitic sclerosis of testicle.

The nodules may remain unchanged for months, or increase in size and become confluent, so that large protuberances are formed, which, because of the distortion of the face that they occasion, have given rise to the designation *facies leontina*.

Through *external influences* ulcers may be produced which show no tendency to heal. New nodules occasionally appear following erysipelas.

Leprosy of the nerves (*lepra nervorum sive anæsthetica*) leads first to hyperæsthesia and pain, later to anæsthesia, more rarely to motor paralyses. Further consequences of disease of the nerves are disturbances which
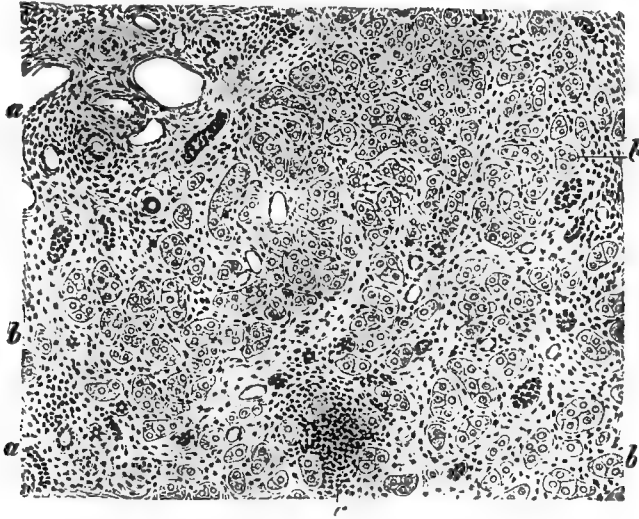
FIG. 452.—Induration of the liver in congenital syphilis (Müller's fluid, hæmatoxylin, eosin). *a*, Hypertrophic periportal connective tissue; *b*, indurated gland tissue infiltrated with connective tissue; *c*, collection of cells. ×100.

express themselves in the skin by the formation of white and brown spots (*lepra maculosa, maculo-anæsthetica, morphæa nigra et alba*), and, in the bones and muscles, by atrophy. Since those suffering from the disease are likely to injure themselves after the appearance of anæsthesia, ulcers
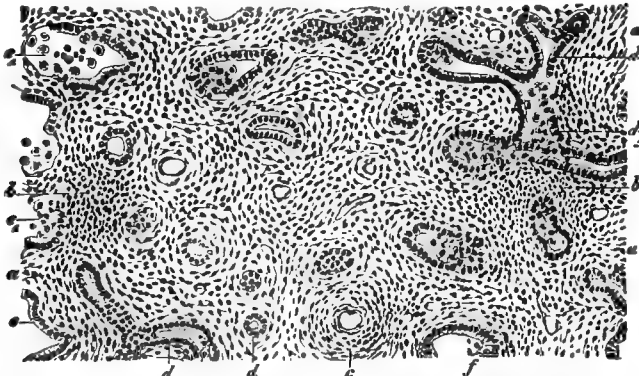
FIG. 453.—Changes in the lung in congenital syphilis (Müller's fluid, hæmatoxylin, eosin). *a*, Proliferating stroma rich in cells; *b*, cellular granulation-foci; *c*, artery with thickened adventitia; *d, d₁*, gland-like bronchi, which in part (*d₁*) contain desquamated epithelium and round cells; *e, e₁*, alveoli, which in part (*e₁*) contain desquamated epithelium and round cells. × 52.

are often formed which cause deep erosions and may lead to the loss of entire phalanges (*lepra mutilans*).

Leprosy of the skin and of the nerves are usually combined; more rarely do they occur alone. Besides the nose, skin, and nerves, the

central nervous system, mucous membranes, cornea, the cartilages, liver, lungs, spleen, lymph-nodes, and testicles, become diseased.

In Europe leprosy is confined mainly to Norway, Sweden, Finland, the Baltic Sea provinces of Russia, and the coasts of the Mediterranean;
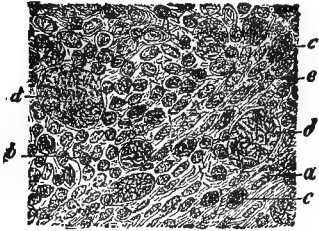
FIG. 454.

FIG. 455.

FIG. 454.—Tissue from a leprous nodule (alcohol, fuchsin, methylene-blue). *a,* Fibrocellular tissue; *b,* round-cells; *c,* medium-sized cells; *d,* very large cells filled with bacilli; *e,* free bacilli. × 200.
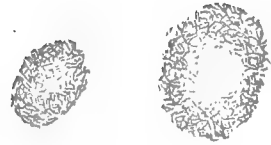
FIG. 455.—Giant-cells with vacuoles containing bacilli, from leprous proliferations of the nasal mucosa (alcohol, Gabbet's stain). × 400.

but occurs sporadically in other regions. It occurs frequently in Hindustan, China, Sumatra, Borneo, Java, and Mexico, on the northern and eastern coasts of South America, in Upper and Lower Guinea, in Cape Colony, and on the northern coast of Africa.
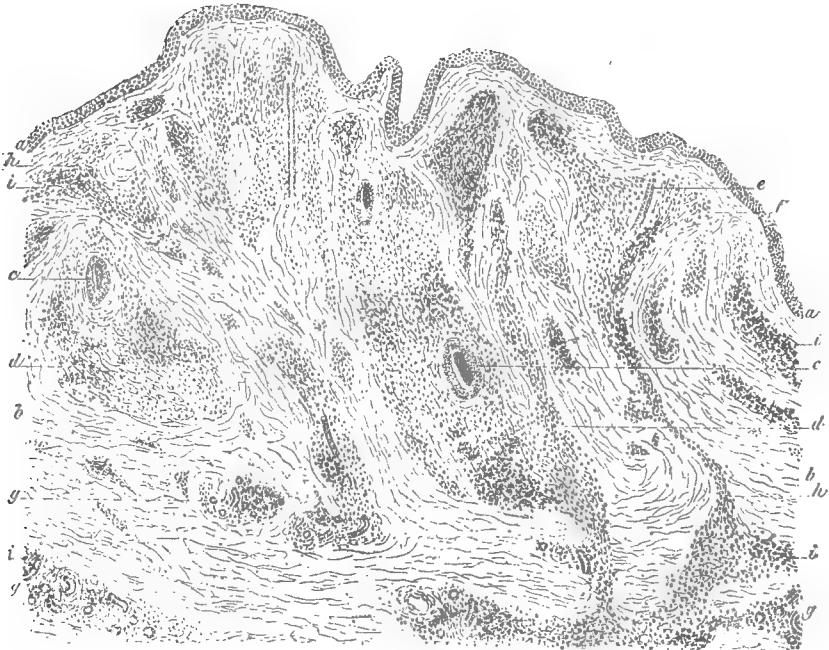
FIG. 456.—Section through a leprous nodule of the skin (alcohol, Gabbet's method). *a,* Epidermis; *b,* corium; *c,* hair-follicle; *d,* leprous focus in the neighborhood of the hair-follicle; *e,* duct of sweat-gland; *f,* leprous nodule about duct of sweat-gland; *g,* leprous foci in the neighborhood of sweat gland; *h,* leprous focus having no especial relation with any of the specific skin structures; *i,* foci of bacilli. × 32.

Leprosy is prevalent in Mexico, the West Indies, and in the Philippines, and cases are found in New Brunswick and other parts of Canada and scattered throughout the United States, the most important centres being in Louisana, California, and Minnesota. According to a Senate report of 1902, there were at that time 278 known cases of leprosy within the borders of the United States.

FIG. 457.—(Bellevue Hospital.) Leprosy in a Filipino, showing the lion-like facies, the macular eruption on the arms and legs, a nodule in the left groin and another on the left forearm. In this patient, leprosy bacilli occurred in the nasal secretions in great profusion.

§ 174. The **Bacillus mallei** was discovered by Löffler, Schütz, and Israël in glanders foci, and later confirmed and studied by Weichselbaum, Kitt, and others. It is the **cause of glanders** (*malleus, maliasmus*) and of *farcy* (*skin glanders, malleus farciminosus*), a contagious disease of horses, which occurs in man chiefly through transmission from horses.

The glanders bacilli are small, slender rods, which occur in the diseased foci, sometimes scattered, sometimes lying in small clumps. Alkaline methylene-blue or gentian-violet is employed for their staining. The bacilli at times appear in the blood (Löffler, Kitt).

The bacilli grow at a temperature of 30°-40° C., on coagulated blood-serum, potato, and agar. On blood-serum they form small yellowish transparent drops which later become milky white. On agar the colonies
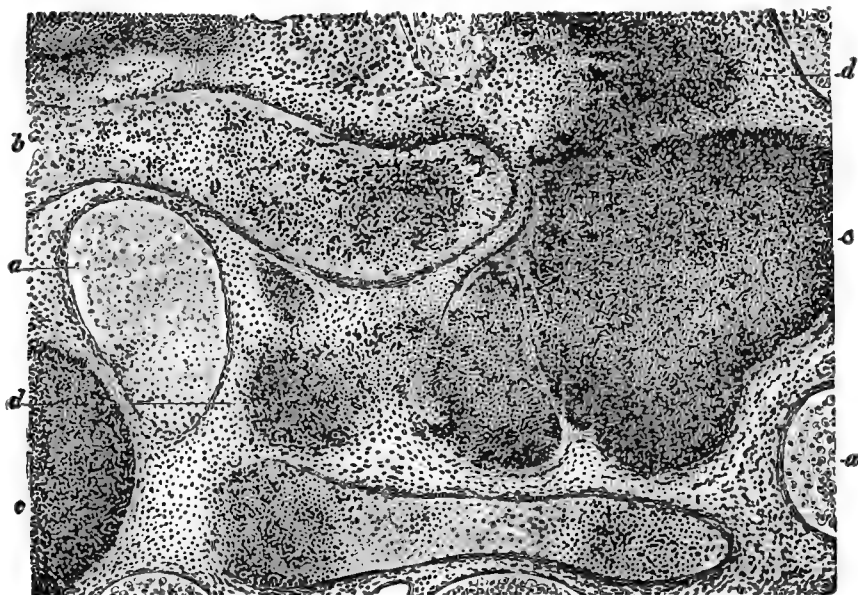
Fig. 458.—Glanders of a cat's testicle (Müller's fluid, hæmatoxylin). *a*, Seminiferous tubules; *b, c,* tubules filled with leucocytes; *d,* foci of leucocytes in the connective tissue. × 90.

are grayish-white. In cultures club-shaped forms and threads are not infrequently seen. Spore-formation has not been demonstrated.

Horses, asses, sheep, young dogs, goats, cats, guinea-pigs, and field-mice are suitable for inoculation. In cats, after inoculation, there develop in the testicles cellular foci consisting of leucocytes (Fig. 458), which lie in the canaliculi (*b, c*) and around them (*d*). The injection of the pus of glanders into the peritoneal cavity of male guinea-pigs causes the testicles to swell rapidly (Straus). This reaction is of great diagnostic value. After subcutaneous inoculation ulcers develop at the seat of inoculation, followed by swelling of the neighboring lymph-nodes. Later, nodules may develop in the internal organs, and ulcers may be formed in the nose. Typical glanders may be produced in horses and asses. Cattle, white mice, and house-mice are immune.

The usual atrium of infection in horses is the mucous membrane of the nose; following this is involvement of the submaxillary glands, and

metastasis in various organs. In the nasal mucosa there arise diffuse cellular infiltration or subepithelial nodules the size of a millet-seed or pea. In chronic farcy larger nodules are developed which join in rows, forming worm-like cords.

The nodules in the mucous membrane break down easily. The cells of which they are composed are for the greater part pus-corpuscles. Through disintegration, softening, and suppuration ulcers with yellowish, infiltrated bases are formed. These enlarge through progressive infiltration and subsequent disintegration of the edges of the ulcer, as well as through confluence of neighboring ulcers. Horses dying of glanders often present in the mucosa of the nasal septum extensive, irregularly shaped, sinuate ulcers, with eroded edges and floors covered with gray and yellowish material. In addition to these there are numerous small, lenticular ulcerations and gray or yellowish nodular foci which are on the point of breaking down. Healing is characterized by the formation of radiating scars.

The cervical lymph-nodes are constantly swollen and inflamed. Of the internal organs the lungs especially are involved. They contain nodules having a caseated centre and a grayish periphery, or foci of lobular pneumonia, which present a gray or hæmorrhagic appearance, or through fatty and cheesy metamorphosis become opaque and yellowish-white. Occasionally the mucosa of the alimentary tract contains nodules of varying size, in part clear gray and consisting of cellular tissue, or opaque yellowish-white, undergoing caseation or approaching suppuration. The spleen, liver, kidneys, and bone-marrow may also contain nodules.

In farcy, which runs a more chronic course than glanders, there are formed in the skin and muscles nodules consisting of small-cell tissue which later undergoes retrogressive metamorphoses, caseates and disintegrates.

In **man infection with glanders** usually takes place through small wounds of the skin, but may occur primarily in mucous membranes adjacent to the skin. In the skin and subcutaneous tissue it gives rise to roseolar spots, hæmorrhages, and papular, nodular, and pustular exanthemata, carbuncular and phlegmonous inflammations which may result in suppuration, and to purulent inflammations of the lymph-vessels and lymph-nodes. In the mucosa of the respiratory tract catarrhs are produced and suppurating nodules and nodes are formed, leaving ulcers behind. In the internal organs metastatic nodules are formed, showing a tendency to suppuration; also abscesses and purulent infiltrations, especially in the muscles. In chronic farcy, which may last for years, large nodules are occasionally formed in the skin and muscles that, through disintegration, give rise to ulcers which heal with difficulty. For diagnosis of the condition bacteriological examination and inoculation experiments are necessary.

According to the investigations of *Kalning, Preusse,* and others, an active poison, *mallein,* may be extracted from cultures of glanders bacilli, that, when injected in small doses into horses sick of glanders, causes a febrile rise of temperature, and may be used as a diagnostic aid.

§ 175. The **Bacillus of rhinoscleroma** is constantly present in the disease known as *rhinoscleroma* or *scleroma respiratorium,* and is regarded as the cause. It stains best with methyl-violet, the sections being left in the stain for twenty-four to forty-eight hours. After staining, the

sections are treated with iodine water, or left in absolute alcohol for one to three days. The bacilli possess a capsule and belong in the Friedländer group.

Rhinoscleroma occurs chiefly in eastern Austria and southwestern Russia; isolated cases have been observed in Silesia, Italy, Egypt, Belgium, Sweden, Switzerland, and Central America. It is a chronic disease beginning in the nose, more rarely in the pharynx, larynx, or palate, and extending thence to neighboring parts — the external nose, lips, lachrymal duct, trachea, etc. In the nose the disease is characterized by thickening of the nasal wall which is sometimes diffuse, sometimes elevated or nodular. The external skin takes on a red or brownish-red color, becomes stiff and fissured and covered with scales. In the throat and respiratory tract dense, cartilage-like infiltrations are sometimes present, at other times contracting cicatricial tissue is formed. The infiltrations appear in the form of nodes and nodules or as elevations and flattened areas of thickening, or may spread out more diffusely. By transformation into scar tissue marked deformities are produced. Deep destruction of

FIG. 459.   FIG. 460.

FIG. 459.—Section of rhinoscleromatous tissue, with numerous degenerated and vacuolated cells containing bacilli (osmic acid, hæmatoxylin). Preparation by Stepanow. × 340.

FIG. 460.—Cells in condition of hyaline degeneration, and hyaline spherules, from rhinoscleromatous tissue of the vocal cord and of the nose. Preparation by Stepanow. *a, b, c, d,* Hyaline-degenerated cells containing small bacilli; *e,* hyaline cells with encapsulated bacilli; *f, g,* cells with hyaline spherules; *h,* free hyaline spherules. *a, b, c, d,* Stained with Löffler's solution; *e,* with hæmatoxylin; *f, g, h,* with fuchsin. × 425.

tissue is absent; superficial ulcerations may, however, occur. On section the infiltrated tissue appears yellowish, or shows a gray or grayish-red color. The affected areas consist partly of granulation tissue, partly of fibrous connective tissue. If the former extends to the epithelial covering there appear proliferation of and degenerative processes in the epithelial cells, the latter being characterized by the formation of vacuoles. The vacuoles often contain bacilli.

The granulation tissue itself shows in many places no peculiarities. In other places, there are found large connective-tissue cells containing one vacuole or showing total vacuolar degeneration or a reticulated structure, in the meshes of which bacilli may be demonstrated (Fig. 459), some possessing capsules.

There also occur cells of various shapes which have undergone hyaline change (Fig. 460, *a, b, c, d, e*). These contain bacilli with and without capsules, and coccus-like forms. Through loss of nuclei these cells may become converted into homogeneous lumps (*d*). Finally, there are cells which enclose hyaline spherules (*f, g*); free spherules are also found lying in the tissues (*h*). In places not yet affected by cicatricial retrogression the hyaline formations may be present in large numbers.

According to *Paltauf, von Eiselsberg, Dittrich, Wolkowitsch,* and others, the bacilli of rhinoscleroma may be cultivated on blood-serum, gelatin, agar-agar, and potatoes, and form capsules in the cultures. When grown in bouillon they show on the contrary no capsules (*Dittrich*). Stab-cultures in gelatin resemble the nail-cultures of the Friedländer pneumonia-bacillus, but are translucent grayish-white and not dead-white. The bacilli stain more easily than the pneumonia bacilli, and are Gram-negative. *Stepanow* observed, in inoculations into the eyes of guinea-pigs, progressive inflammation and pro-liferating granulations containing bacilli and hyaline cells.
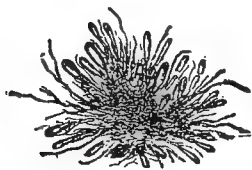
FIG. 461.

FIG. 462.

FIG. 461.—*Actinomyces hominis.* Teased preparation. × 700.
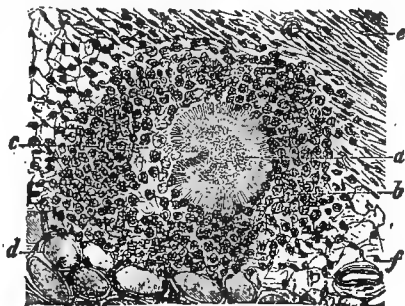
FIG. 462.—Actinomycosis of the tongue (alcohol, alum carmine.) *a,* Actinomyces; *b, c,* cellular nodules; *d,* transverse section of muscle; *e, f,* connective tissue with blood-vessels. × 175.

§ 176. The **Actinomyces** or **ray-fungus** is a fission-fungus which appears in different forms of growth in the human and animal organism
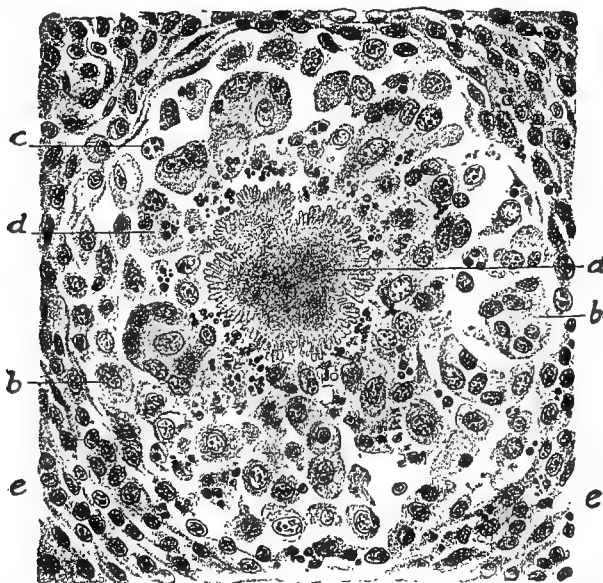
FIG. 463.—Actinomyces, surrounded by epitheloid and pus-corpuscles (alcohol, hæmatoxylin, eosin.) *a,* Fungus; *b,* mononuclear and multinuclear epithelioid cells; *c,* pus-corpuscles; *d,* phagocyte, enclosing a pus-corpuscle; *e,* granulation tissue. × 500.

and in cultures. It is the cause of **actinomycosis**, a disease occurring in man and in cattle, swine, and horses, more rarely in sheep, dogs. and

cats, and characterized by progressive inflammation that produces granulation and connective tissue, and pus. The botanical position of the fungus is unsettled. By many it is classed with the *thread-fungi,* others group it with the *polymorphous bacteria.* Boström places it in the group *cladothrix;* Kruse, among the *streptothrix.*

According to the investigations of Boström actinomyces differs from bacilli in that in cultures on beef's-blood serum or agar it forms *branching threads.* The threads are straight or wavy, at times twisted spirally.
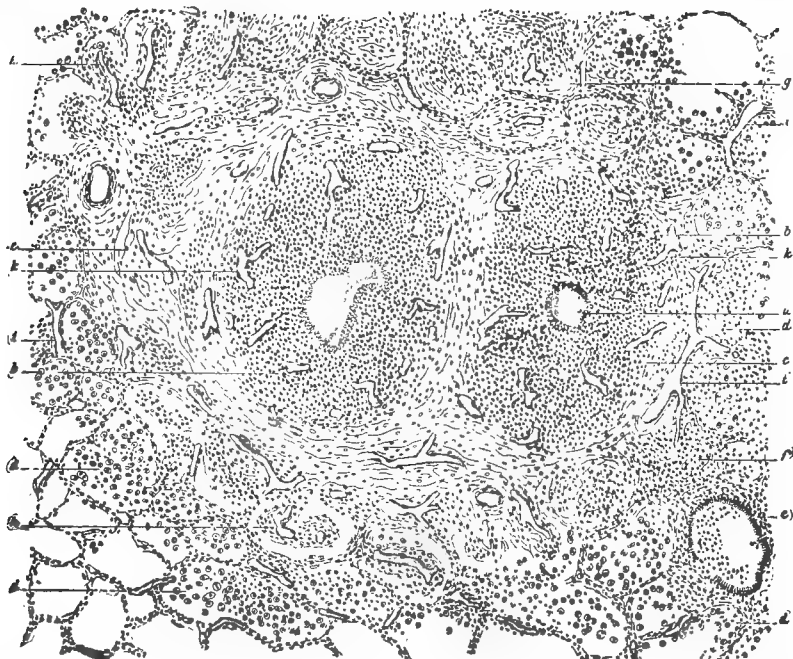
Fig. 464.—Actinomycosis of the lung (alcohol, carmine, Gram's). *a,* Fungus; *b,* small-cell nodule; *c,* fibrous tissue; *d,* alveoli filled with large and small cells; *e,* bronchiole with wall infiltrated with cells; *f,* small-cell focus in the neighborhood of the bronchus (*e*); *g,* alveoli filled with vascularized connective tissue; *h,* connective tissue growing into the alveoli; *i,* blood-vessels of the lung tissue; *k,* blood-vessels of the inflamed area. × 42.

They break up by transverse division into short rods and coccus-like forms, which under suitable conditions again grow into threads.

Within the human and animal organism the fungus appears in the form of granules scarcely recognizable by the naked eye, or in spherules up to 2 mm. in diameter. These are sometimes colorless and transparent, at other times white and opaque, sometimes yellow, or brown, or green and yellowish-green. Many of the smaller ones consist of a feltwork of fine, partly branched threads, which are straight, wavy, or twisted. The majority of the granules contain peculiar club-shaped structures (Fig. 461), which form the ends of the threads, and if present in large numbers have a radial arrangement (Figs. 462, *a;* 463, *a*), and give to the fungus a ray-like appearance. Occasionally hand-shaped or fan-like forms develop on the ends of the threads. According to Boström, these peculiar structures are due to swelling of the membrane of the threads, and are retrogressive changes.

The actinomyces is usually taken into the body with the food or respired air, and often first develops in the tissues of the mouth, gums, tongue, etc. Not uncommonly club-shaped forms are to be found in the crypts of the tonsils in individuals in whom there is no indication of actinomycosis. The fungus has not been demonstrated outside the human and animal organism. It must be remarked that often bits of higher plants have been found in the pus of actinomycotic foci, and that the swallowing of portions of plants or the contamination of wounds with vegetable material, have preceded the development of actinomycosis. It is, therefore, probable that the fungus is present on the higher plants or on wood. Johne demonstrated it as early as 1882 on beards of wheat found in the tonsils of swine.

If the ray-fungus lodges in a tissue it excites inflammation in the neighborhood. While the fungus which has penetrated into the tissue develops a mycelium and a fungus-granule (Figs. 462, *a;* 463, *a;* 464, *a*) there is formed in its neighborhood a nodular focus of inflammation, which at first consists of leucocytes (Figs. 462, *b, c;* 464, *b*), and later (Fig. 463, *c*) contains epithelioid and giant-cells (*b, d*).

The fungus-granules may increase in the nodule and lead to its enlargement; it often happens that cellular nodules contain a large number of fungus-foci, which are usually situated at the periphery. New fungus-foci, and consequently new cellular foci, appear in the neighborhood. The further spread of infection takes place by means of small rods and threads, which are broken off from the larger masses, and may be seen in the tissues free and enclosed in cells.

Larger nodules often undergo purulent liquefaction of their central portions, with the formation of small *abscesses,* which become confluent to form *pus-cavities,* or rupture and lead to *sinuses.* In the neighborhood of the purulent areas (Fig. 464) there is active *proliferation of tissue,* the *formation* of *vessels* (*k*) and young *granulation tissue,* which later becomes transformed into cicatricial *tissue* (*c, g, h*). If connective-tissue proliferation attains considerable proportions, it leads to *induration* (Fig. 464), often to *enlargement of the part.* The connective-tissue may extend into the small-cell areas, and replace them, the fungi probably being destroyed in this way.

Predominance of tissue-necrosis and suppuration over tissue-production gives rise to sinuous cavities and fistulous tracts communicating with one another or with the exterior. The walls consist of granulation-tissue and hyperplastic connective tissue, and here and there contain fungus-foci. The masses of fungi may become partly calcified.

In cattle the disease affects chiefly the lower jaw, but may involve the upper jaw, the tongue, throat, laynx, œsophagus, stomach, intestinal wall, skin, lungs, and subcutaneous and intermuscular tissues; in *swine* it is found in the udder and different bones of the skeleton, while in *horses* it occurs chiefly in the vas deferens following castration. In cattle it leads to more or less extensive fibrous tumors containing purulent foci, and was formerly given various names, such as osteosarcoma, bone-cancer, bone tuberculosis, lumpy jaw, wooden tongue, tuberculosis of the tongue, lymphoma, fibroma, worm-nodules, etc.

In *man* infection takes place through the mouth, fauces, œsophagus, stomach, intestine, and lung, or by external injury. In the mouth infection may take its start from carious teeth, or from injury to the soft parts of the jaw or cheek. Thence it spreads and may finally involve the

face and the hairy portions of the head, as well as the throat, neck, back, and breast.

With the advent of actinomycosis there arise swellings which soften and give fluctuation. When the latter is the case, pus is formed which is at times thin and watery, at other times more viscid, and contains the characteristic granules. If the abscesses break externally there may be formed fistulous tracts, which either close again, or continue to secrete pus.

Besides the purulent foci, which sometimes are small, at other times extensive, granulation tissue arises and may be abundant. As a result of fatty degeneration and disintegration of its elements the granulation tissue often becomes whitish or yellowish or reddish-white in color, and permeates the diseased tissue in an irregular manner. In other places it develops into connective tissue, particularly in those places where the process is not spreading.

Through development of connective tissue local healing resulting in cicatricial induration may take place, but in other parts the process makes further progress and may lead to extensive destruction. If the disease encroaches on the bones of the spinal column or of the thorax these may be gradually destroyed, and become eroded and carious. In rare cases the jaw-bone may be attacked from within through the alveolar process, and so undergo destruction. From the base of the skull infection may extend into the interior and lead to actinomycotic meningitis and encephalitis.

In primary infection of the respiratory apparatus the process takes the form of bronchopneumonia characterized by the formation of nodular foci (Fig. 464, *b*) the central portions of which at an early stage assume a yellowish-white color. Through disintegration of the inflammatory foci cavities may be formed which contain fluid, pus-corpuscles, fatty detritus, spherules of fatty granules, disintegrated red cells, and masses of actinomyces. The tissue lying between the mycotic foci suffers more or less extensive, often marked, inflammatory thickening (Fig. 464, *c*), and may thus be transformed into a slate-gray or gray and white mass, devoid of air, later undergoing cicatricial contraction. In this manner a large portion of the lung may be replaced by scar tissue.

From the lung the process sooner or later extends to the visceral pleura, from this to the costal pleura or pericardium, giving rise to inflammatory exudations and proliferations of tissue, which lead to adhesions between the opposite layers. From the costal pleura cellular infiltration, pus formation, and fatty degeneration and disintegration of the granulation tissue may extend between the ribs and spread in the connective tissue and muscles, and finally break through the skin. From the lungs rupture may take place into the mediastinum or pericardial sac, and finally into the heart, or through the diaphragm into the abdominal cavity, or from the posterior mediastinum into the retroperitoneal connective tissue.

The secondary areas of destruction lying outside the lung often reach an extremely large size, while in the lung the primary process advances but little and may even undergo cicatrization. At one time softening predominates, at another time the formation of granulation tissue and induration.

Primary actinomycosis of the intestinal tract begins with the formation of plaque-shaped whitish patches or of nodular mucosal and sub-

mucosal foci, which contain the specific fungus, and lead to ulceration. From the intestine the process spreads over the peritoneum and through the retroperitoneal connective tissue, as well as to adjacent organs — for example, the liver; and may finally break through the abdominal wall.

Metastasis may be associated with local progression of the disease, but is rare. It usually results from direct rupture into a blood-vessel. The metastases arising from a primary focus in the intestine are found especially in the liver; those arising from a primary focus in the lungs are found in the skin, muscles, bones, brain, intestine, and kidneys. The metastatic nodules behave like the primary foci. In rare cases there occur primary foci of actinomycosis in the internal organs — for example, in the brain and liver. The portal of entrance in these cases may not be demonstrable.

Johne, Ponfick, Boström, Wolff, and Israël attempted inoculation experiments in animals, and according to their reports obtained positive results (Johne, Ponfick, Wolff, and Israël). Wolff and Israël, by inoculation of rabbits and guinea-pigs, reproduced a characteristic disease with the formation of inflammatory foci containing the fungus-masses. They were also able to cultivate the fungus from these foci.

Levy, as well as *Kruse,* assumes that there are two forms of actinomyces, an aërobic cultivated by *Boström* and an anaërobic cultivated by *Wolff, Israël, Aschoff,* and himself, the two forms being closely related. *Mertens* announces that he succeeded in changing the Wolff-Israël form into the Böstrom. Levy regards the *actinomyces* as well as the fine-threaded fungus known as *streptothrix* as belonging to a group, the *Hyphomycetes,* characterized by the formation of branching, probably unicellular mycelia and which multiplies through acrogenic snaring-off of conidia-chains or through fragments of threads resembling bacilli. Since the ray-fungi do not correspond to any one of the known hyphomycetes-groups, he places them in a separate group, the **Actinomycetes.** In this group he also places the tubercle-bacillus, the lepra-bacillus, the diphtheria-bacillus, and the bacillus of glanders. *Lubarsch* regards the streptothrices, with which he classes the ray-fungi (to which the tubercle-bacillus also belongs), as a transition form between the bacilli and the moulds.

Berestnew distinguishes different forms of actinomyces (cultivated by him from hay, straw, etc.), and, in addition to *actinomycosis,* recognizes a variety of pseudo-actinomycosis, which runs a similar course to that of the former, but is caused by fungi which do not belong to the ray-fungi. *Krause* and *Gilbert* likewise regard the etiological factor of actinomycosis as being of varied nature and not representing a definite entity. *Schürmayer* emphasizes the variability of actinomyces according to the conditions of growth. *Wright* believes that human and bovine actinomycosis are identical, and holds that there is but one species of microorganism (*Actinomyces bovis*) concerned in the production of actinomycosis. The lesions produced by other forms of branching organisms he would class under the head of *nocardiosis,* reserving the term actinomycosis for those conditions in which characteristic "drusen" are formed.

Petruschky unites Actinomyces, Streptothrix, Cladothrix, and Leptothrix into one family, which he calls **Hair fungi** or **Trichomycetes.** These he groups with the hyphomycetes, of which he distinguishes two great classes, the mould fungi and the hair fungi.

Actinomyces is characterized by radiating forms; *streptothrix* by true branching, late fragmentation of the wavy threads and the formation of conidia; *cladothrix* by false branching of the threads (lateral direction of the membrane with continuation of the longitudinal growth in the other direction) and rapid fragmentation of the threads; while *leptothrix* is characterized by stiff threads without branching.

There occur numerous observations in which organisms apart from the actinomyces described above and belonging to the **trichomycetes,** particularly to the *streptothrices,* gave rise to local-tissue changes, particularly purulent and granu-

lating inflammations, and also to tubercle-like changes, but in many cases the authors are not agreed as to what species the fungus concerned belonged.

As early as 1855 fungus masses were observed by *von Graefe* in the inflamed lachrymal duct. These were at first regarded as favus, but later *Cohn* (1874) regarded them as streptothrix and gave them the name *Streptothrix foersteri*. Likewise *Axenfeld,* who has many times cultivated the fungus, regarded it as a variety of streptothrix.

Under the term *Cladothrix asteroides, Eppinger* described a polymorphous fission fungus or hair fungus found in the pus of an old cerebral abscess causing death through meningitis. Since in the affected individual changes similar to tuberculosis were found in the lungs and bronchial glands and since inoculation of guinea-pigs and rabbits gave rise to a disease resembling tuberculosis, he designated the disease produced by the fungus as *Pseudotuberculosis cladothrichica*. *Mac-Callum* regards Eppinger's fungus, which he obtained from a purulent peritoneal exudate, as belonging to the Actinomyces group and calls it *Actinomyces asteroides*. *Schabad* regards a fungus characterized by branching threads which he found in a subpectoral abscess, and according to its behavior in cultures apparently identical with the Eppinger fungus, as belonging to the actinomyces group, and designates it atypical actinomyces, which differs from the typical form in that it produces no clubs and is acid-fast. In animals it causes pseudotuberculosis.

Buchholtz found a variety of streptothrix in a pneumonic lung containing large cavities with ragged walls. *Langer* found a streptothrix pathogenic for guinea-pigs in the sputum of a thirteen-year-old-boy that probably arose from an œsophageal diverticulum.

According to investigations by *Kanthack, Boyce,* and *Vincent* it is probable that the disease occurring in India known as **Madura-foot** or **Mycetoma,** characterized by gradual swellings in the extremity, with nodular deposits becoming changed into abscesses and fistulous tracts through suppuration, and on pressure discharging purulent gray, or brown to black, fish-roe or truffle-like granules is caused by a polymorphous *fungus related to Actinomyces* and designated by *Vincent* as *Streptothrix maduræ*. *Kanthack* regards the fungus which is enclosed in the granules as identical with Actinomyces, but the investigations of *Vincent* and *Boyce* do not agree with this assumption. According to *Boyce,* the *Streptothrix maduræ* occurs in two varieties, one white or yellow, with fine dichotomous branching threads, and one black, with branched pigmented threads. *Unna* and *Delbanco* also distinguish different fungi which they class with the Actinomyces. According to *Oppenheimer* mycetoma is a granuloma with abscess formation caused by two kinds of fungi; the yellow form is an actinomyces, while the fungus of the black form cannot at present be classified, but probably belongs to the oïdia or moulds. The parasite of the madura disease has been known since the year 1874 (*Carter, Lewis,* and *Cunningham*), and was formerly called *Chionyphe Carteri*.

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3. The Spirilla and the Diseases Caused by Them.

(*a*) *General Remarks on the Spirilla.*

§ 178. The **Spirilla,** or **Spirillaceæ,** or **Spirobacteria** are divided into two genera, one of them called *Spirillum,* the other *Spirochæte.* Many writers recognize still another genus, *Vibrio.*

The genus **Spirillum** is characterized by the formation of short, stiff, shallow spirals, which possess flagella and show active swarming movement. The wavy rods are called **vibriones** by many writers.

The genus **Spirochæte** is characterized by long, flexible, or closely turned spirals.

(*b*) *The Pathogenic Spirilla.*

§ 179. The **Spirillum Choleræ asiaticæ,** *Vibrio choleræ,* or *comma-bacillus,* was discovered by R. Koch in 1884, and is the cause of Asiatic cholera. The spirilla (Fig. 465) form small *comma-like, curved rods,* from 0.8–2 μ long.

FIG. 465.—Cholera-spirilla from a pure culture. Cover-glass preparation stained with fuchsin. × 400.

Cultures of cholera-spirilla may be obtained on a great variety of media of slightly alkaline reaction. The temperatures most favorable for their development lie between 25° and 30° C.; between 16° and 8° C. they are still capable of feeble development.

In fluid media in the presence of oxygen they show lively movements that may be easily observed in the hanging drop. The movements are produced by means of a *terminal flagellum.*

Cholera spirilla are often destroyed by the gastric juice, but escaping this and gaining entrance to the *intestinal tract of man* they develop both in the small and large intestines, and multiplication is followed by transudation from the intestinal mucosa, so that the intestine becomes filled with a fluid resembling meal-soup or rice-water due to flakes of desquamated epithelium.

The spirilla are always present in great numbers in the intestinal contents, and are found in the lumina of the intestinal glands, whence they may penetrate between and beneath the epithelial cells.

In recent cases the spirilla may be demonstrated in cover-glass preparations stained with methylene-blue or fuchsin. Fresh dejecta, as well as soiled linen, are suitable for the examination, since, according to observations made by Koch, the spirilla may multiply actively for some

time on moist linen and moist earth. In old cases the demonstration of spirilla is more difficult, and is attainable most surely by plate-cultures.

The *presence of cholera-spirilla in the intestine excites inflammation,* which finds expression in redness, swelling, marked transudation, mucoid degeneration of epithelium, and desquamation; later, by hæmorrhages, sloughs, and ulceration. It is characterized constantly by more or less marked cellular infiltration of the tissues. The solitary follicles and Peyer's patches are swollen, even in fresh cases. Death may take place after a few hours or after one to three days. If the disease lasts a longer time, the intestinal contents become more consistent and the intestinal mucosa shows ulcerative changes.

According to our present knowledge, the spirilla produce substances which cause local damage to the mucosa of the intestinal canal, and when absorbed give rise to symptoms of intoxication and paralysis of vessels. Small foci are often present in the liver and kidneys, in which the gland-cells show cloudy, fatty, or hyaline degeneration, or are necrotic. More-over, the kidneys frequently show cloudiness caused by degeneration of the epithelium. Ecchymoses in the epicardium are frequent; in the later stages patches of necrosis may occur in the mucous membrane of the vagina. Finally, the spirilla may be crowded out by putrefactive bacteria in the intestine, and through absorption of products of decomposition intoxication may arise, which is not dependent on the original spirilla.

Cholera-spirilla may also be found in the vomitus, and in the ductus choledochus and gall-bladder. The spirilla do not usually enter the blood, but in cases of severe infection may spread throughout the body.

Koch demonstrated the presence of spirilla in a tank in India which furnished the inhabitants of the region with water for drinking and other purposes, at a time when part of the inhabitants were sick and dying of cholera. Since then, spirilla have often been demonstrated in water-supplies during cholera epidemics.

Asiatic cholera is endemic in Lower Bengal. Thence it spreads at times throughout India. Since the spirilla are easily killed outside the body transportation must be effected mainly by individuals suffering from the disease. The infection probably occurs exclusively through the alimentary tract, as the result of the introduction of infected beverages, food, or other substance into the mouth; but not every introduction of cholera-spirilla into the digestive canal is followed by infection due, most likely, to the destructive action of the gastric juice.

Moreover, it not infrequently happens that the spirilla increase in the intestine, but excite only slight changes, so that the infected individual suffers no marked symptoms, and the diagnosis can be made only through the demonstration of spirilla in the stools.

If cholera-spirilla get into the water-supply and increase, cholera may develop in the region with great rapidity. If, on the contrary, infection takes place by contagion from man to man, the spread is slow, in that the disease is confined to those who come in contact with the sick, or with contaminated articles. The incubation period is from one to two days.

In the intestines of convalescents the spirilla may live for a long time and multiply without giving rise to any symptoms betraying their presence. Kolle was able to demonstrate them in a number of cases after five to eighteen days, and even as long as twenty to forty-eight days.

One attack of cholera makes the individual immune for a certain time. The immunity depends on the presence of bactericidal anti-bodies.

On gelatin-plates **cholera-spirilla** form round, flat, yellowish discs which liquefy the gelatin slowly. At low magnification the colonies are irregular in outline, and of a granular or furrowed and rough surface, as if strewn with small particles of glass (*Koch*). Through liquefaction of the gelatin there is formed in its immediate neighborhood a funnel-shaped cavity, to the bottom of which the colony sinks.

Stab-cultures in gelatin form on the second day a whitish cord corresponding to the stab, in the immediate neighborhood of which the gelatin is liquefied. The canal thus formed widens above into a funnel part which is filled in its lower portion with liquefied gelatin and in its upper part with air. The widening of the funnel takes place slowly, so that its edge reaches the wall of the tube only after five to six days.

On potatoes at from 30°-35° C. the spirilla form light-brown cultures, on agaragar grayish-yellow slimy cultures. They grow also in bouillon, blood-serum, and milk.

They do not increase in pure water (*Bolton*), but do so in water contaminated with substances furnishing nutrient material.

The cholera-spirilla are aërobic, but are also able to grow under anaërobic conditions. According to investigations by *Hueppe*, cultivation with a deficient supply of oxygen increases the virulence of the culture; but the resisting power against injurious agents — for example, against acids — is lowered; with free access of oxygen the reverse takes place. *Pfeiffer*, however, found that young cultures grown in the presence of oxygen also contained poison. The spirilla present in fresh dejections (*Hueppe*) are easily killed, and have but little infecting power; whereas growth of the spirilla outside the body increases their resistance (for example, against the gastric juice) and makes them more capable of causing infection in new individuals. They are easily destroyed by desiccation in free air (*Guyon*), by high temperatures, and by boiling for a short time. They are easily supplanted by saprophytic bacteria when the nutrient material and the temperature are not suitable. In the contents of privy-vaults they soon die out (*Koch*). They are easily killed by acids, mercuric chloride, and carbolic acid. According to *Koch*, they may live in well water for thirty days, in sewage for seven days, and on damp linen for three to four days. *Nicati* and *Reitsch* found them alive after eighty-one days in water taken from the harbor of Marseilles.

In cultures they sometimes form short rods, more or less curved (Fig. 465) and often joined in pairs; at other times they form long spirals. With these there also occur straight rods, and occasionally the majority form rods which show the curve only imperfectly or not at all.

At a certain degree of exhaustion of the food-material there frequently appear involution forms, in which the rods are sometimes shrunken, sometimes swollen, thus creating a variety of forms. Globular swelling, as well as the formation of spots which do not take the stain in stained preparations, occurs as the result of degeneration, and have been erroneously interpreted as phenomena of fructification. Spore formation has not been demonstrated. The addition of hydrochloric or sulphuric acid to cultures of cholera-spirilla in peptone-containing media (peptone-meat-infusion or an alkaline, one-per-cent solution of peptone containing one per cent of salt) causes the culture to assume a rose-red or Burgundy-red color, due to the formation of coloring-matter, *cholera-red*. According to *Salkowski*, this is a nitrosoindol reaction.

In order to facilitate the separation of cholera-spirilla from other intestinal bacteria, *Schottelius* recommends mixing the dejecta with double the amount of a slightly alkaline meat-infusion, and allowing the mixture to remain uncovered for twelve hours at a temperature of from 30°-40° C. The spirilla requiring oxygen will develop on the surface, and may be transferred thence to plate-cultures. *Koch* recommends for this purpose a solution of peptone with common salt.

According to *Nicati, Rietsch, von Ermengem,* and *Koch,* symptoms resembling cholera may be produced in experimental animals through the introduction of cholera-spirilla into the intestinal canal. This experiment succeeds when cultures are introduced directly into the duodenum or small intestine (*Nicati* and *Rietsch*); as well as when the gastric juice of the animals (guinea-pigs) is neutralized with a five-per-cent solution of soda, the bowels being quieted by an injection of 1 c.c. of tincture of opium to every 200 gm. of the body-weight, and one or more drops of a pure culture of the spirilla then introduced into the stomach (*Koch*).

The animals thus inoculated die with symptoms of collapse. The small intestine is found to be filled with a watery, flocculent, colorless fluid containing spirilla in great numbers; the intestinal mucosa is reddened and swollen.

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The poison which is produced by the cholera-bacillus and which causes the clinical symptoms of infection is not known. *Gamaleïa* believes that it is a nucleo-albumin; *Scholl,* that it is a peptone (choleratoxopepton). *Pfeiffer* is of the opinion that it is an element of the cell-body. According to Metschnikoff and others, it is secreted by the cells. According to *Oppenheimer,* it is probably an *endotoxin* which is labile and easily passes over to a secondary poisonous mixture rich in toxoids. Further, the spirilla contain a *protein which is not specific and which excites inflammation.*

The *virulence of cholera-cultures differs greatly,* according to the place of origin and the age. Virulence decreases with age. Guinea-pigs, which are susceptible to intraperitoneal inoculations of cholera, may be protected against infection by the intraperitoneal injection of attenuated cultures; but no absolute immunity can be produced in this way. The blood-serum of human individuals that have recovered from an attack of cholera shows protective properties for guinea-pigs for several weeks after the attack.

The nitroso-indol reaction in cultures of the cholera-spirilla is due to the fact that the cholera-spirillum in pepton solutions not only forms indol but also nitrites. The addition of hydrochloric or sulphuric acid sets free nitrous acid which forms a red color with indol. With the *Spirillum of Finkler, the Spirillum of Metschnikoff,* and the *Spirillum of Deneke,* which also produce indol, the red color of the cultures occurs only when potassium nitrite is added with sulphuric acid, or when nitrous acid alone is added.

Spirilla Resembling the Cholera-Spirillum.

(1) The *Spirillum of Finkler and Prior,* was found by these observers in the dejecta of persons suffering from cholera-nostras, after the discharges had stood for some time in a vessel. The spirilla are similar to the cholera-spirilla, only somewhat longer and thicker. In plate-cultures they are distinguished from the latter only in the fact that the small colonies are not distinctly granular and have a sharp contour. Gelatin is quickly liquefied; and in stab-cultures after twenty-four hours a sac-like tube filled with cloudy fluid is formed, which soon reaches the walls of the tube.

On potatoes (*Flügge*), even at room temperatures, they form within forty-eight hours a grayish-yellow, slimy coating, sharply marked off from the substance of the potato by a whitish border; while cholera-spirilla do not grow at room-temperature, and at higher temperatures form brown coatings.

Further, they cause foul-smelling decomposition; and are rather resistant to drying. When introduced into the intestine of guinea-pigs by the method given above, they produce effects similar to those caused by cholera-spirilla, but less intense.

It is doubtful whether the *Spirillum of Finkler and Prior* possesses a pathogenic significance for cholera-nostras, since the dejecta from which these investigators obtained their cultures were not fresh; and other authors have failed to find the spirilla in corresponding cases (*Kartulis,* "Zur Aetiologie der Cholera nostras," *Zeitschr.. f. Hyg.,* vi., 1889). *Knisl* (*Münchener ärztliches Intelligenzblatt,* 1885), on the other hand, found them in the cæcal contents of a suicide.

(2) *Spirillum tyrogenum,* found in cheese by *Deneke* (*Deut. med. Wochenschr.,* 1885), is also much like the cholera-spirillum, but somewhat smaller, and the long spiral threads are more closely wound. Cultures on gelatin-plates form sharply contoured discs that by low magnification appear dark, and liquefy the gelatin more rapidly than the spirillum of Koch. In stab-cultures they behave like the Finkler-Prior spirillum, but do not grow on potato.

(3) *Vibrio of Metschnikoff* (*Gamaleïa,* "Vibrio Metschnikovi et ses rapports avec le microbe du cholera asiatique," *Annal. d. l'Inst. Past.,* ii., 1888; iii., 1889; *Pfeiffer,* "Ueber den Vibrio Metschnikovi und sein Verhältniss zur Cholera asiatica," *Zeitschr. f. Hyg.,* 1889) is a fission-fungus isolated by Gamaleïa in an epidemic disease occurring in chickens in Odessa, characterized by diarrhea and enteritis. When cultivated it shows a great resemblance to the cholera-spirillum of Koch. The spirillum is most easily obtained pure by inoculating pigeons with the blood of diseased chickens. The pigeons die in from twelve to twenty hours and show the spirilla in the blood and in the intestinal tract.

Ziegler has transferred **Relapsing Fever** to the protozoan diseases, following *Schaudinn's* view that the spirochætes are protozoa. If this opinion be correct, **Syphilis** should likewise be classed with the protozoan infections. As mentioned below, the correctness of such a view is doubted by other writers (*Novy*), who believe that the spirochætes are bacterial and are to be classed with the spirilla.

CHAPTER XI.

The Yeasts and Moulds, and the Diseases Caused by Them.

§ 180. The **yeasts** (**Blastomycetes**) and the **moulds** (**Hyphomycetes**) belong, as do the schizomycetes, to the non-chlorophyllaceous thallophytes. With the schizomycetes they have no phylogenetic relationship; on the other hand, they are closely related to one another, and both belong to the branching fungi or the eumycetes.

The moulds and yeasts, like the schizomycetes, derive their nourishment from organic substances containing carbon. The majority find their food in dead organic substances, and belong therefore to the *saprophytes;* some are able to obtain nourishment from living tissues, and are to be classed, at least at times, with the *parasites*. In human beings both forms occur.

Outside the organism the moulds are generally known as producers of the different mouldy films which so frequently develop on organic substances. They belong to different groups of fungi. The yeast-fungi are the cause of alcoholic fermentation, and form the scum on the top of alcoholic beverages.

§ 181. **Yeasts** occur in man in the form of *naked* or *encapsulated, oval* or *round cells* of varying size. They are found chiefly as harmless **saprophytes**, most frequently in the upper part of the intestinal canal — in the stomach — where they are almost constantly present; when beverages in the process of alcoholic fermentation are taken they occur in large numbers, and may multiply. In the bladder they may likewise multiply if the urine contains sugar; and may cause fermentation of the urine with evolution of carbonic-acid gas.

Fig. 466—*Saccharomyces ellipsoideus.* × 400.

As **parasites** no importance was attached to them until recently, but the investigations of Busse, Buschke, Sanfelice, Curtis, and others have established the fact that there are *species of Saccharomycetes of pathogenic importance*. According to these observations the pathogenic yeasts multiply in different tissues, in the skin, periosteum, lungs, and glandular organs, and excite *purulent inflammations,* or *proliferations of granulation tissue,* which run a course similar to that of infection with actinomycosis or tuberculosis. In inflammatory foci the yeast cells are for the chief part provided with a capsule.

In solutions containing sugar the blastomycetes form oval cells (Fig. 466). Reproduction takes place through budding and constriction; on any portion of the parent cell there may develop on excrescence, which is constricted off after it reaches the size of the mother cell. The cells may grow out into threads or **hyphæ,** but in these threads no subsequent segmentation occurs; jointed threads arise through budding. A dilute culture-medium favors the formation of threads.

Mould-fungi are found in man in the form of simple or branched, unjointed or jointed threads of varying thickness; and as oblong or

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spherical cells. The threads are designated **hyphæ** (Figs. 467, 468), and the mass which they form as **mycelium;** the spherical or long oval or short cylindrical cells, which are frequently arranged in the form of a rosary, as *spores,* or better as **conidia-spores** (Figs. 467, 468). Only rarely has there been observed in the body fructification on special organs.

The moulds are partly **saprophytes** and partly **parasites;** and are found almost exclusively in regions accessible from without, as the skin, intestinal canal, respiratory tract, external ear, vagina, etc. Only exceptionally do they reach the internal organs, for example, the brain. On the whole, the living tissues of the human organism do not afford a suitable nutrient medium for the mould-fungi, and the life-activities of the tissue-cells do not permit their development and multiplication. The need for oxygen prevents the growth of moulds in many tissues; and for many the temperature of the body is too high.

Moulds growing as saprophytes occur in man most frequently in the alimentary canal, particularly in the *mouth, pharynx,* and *œsophagus.* They develop in these regions particularly when the ingesta or desquamated cells lie undisturbed in one position for a long time, and when the function of the organ concerned is lowered. They are recognized through the formation of hyphæ and conidia.
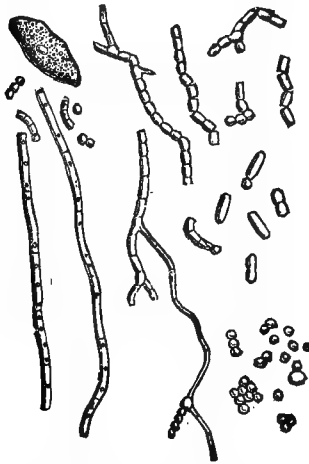
FIG. 467.—Fresh favus-mass consisting of hypæ, conidia, and epithelial cells. (After Neumann.)
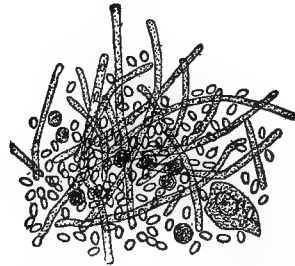
FIG. 468.—From a growth of thrush on the tongue of a man dying of typhoid fever. × 275.

In the external *auditory canal* moulds may grow in masses which fill the passage and consist of cerumen, or of inflammatory exudates and desquamated cells, and of substances introduced from without.

In the *lungs* moulds are occasionally found on the necrotic walls of cavities, particularly those due to tuberculosis, in necrotic and gangrenous infarcts, etc. In the air-passages they are observed most frequently in bronchiectases.

In the alimentary tract, and in the ear and lungs, the moulds form a whitish deposit on or in the tissues. In the event of fructification on special fruit-bearers they take on a brown, gray, or even black appearance. In the intestinal canal the food and drink may give them various colors.

At first the moulds grow in dead material, but may penetrate thence into living tissue; cases have been observed in which they entered the circulation and were carried to distant organs.

The fungous growth called **thrush,** which appears chiefly on the mucous membrane of the *mouth, pharynx,* and *œsophagus,* more rarely on that of the *stomach, intestine,* and *vagina,* and on the *nipples* of nursing women, cannot be regarded as a pure saprophytic, but as a **parasitic growth,** which penetrates living epithelium (Fig. 469, *c*), and even the underlying connective tissue. It is true that thrush occurs chiefly in infants and in debilitated invalids who are no longer able to cleanse the mouth, throat, and œsophagus, so that some local predisposition appears to be necessary for its development; thus it is probable that primary colonization of the fungus takes place in dead material. Nevertheless, penetration into living tissue occurs — first, into the epithelium (*c, d*), but often into connective tissue (*a, f*), and blood-vessels, and from these portals of invasion metastases may develop in the internal organs. Thus, Zenker observed hyphæ and conidia in an abscess of the brain; and Paltauf
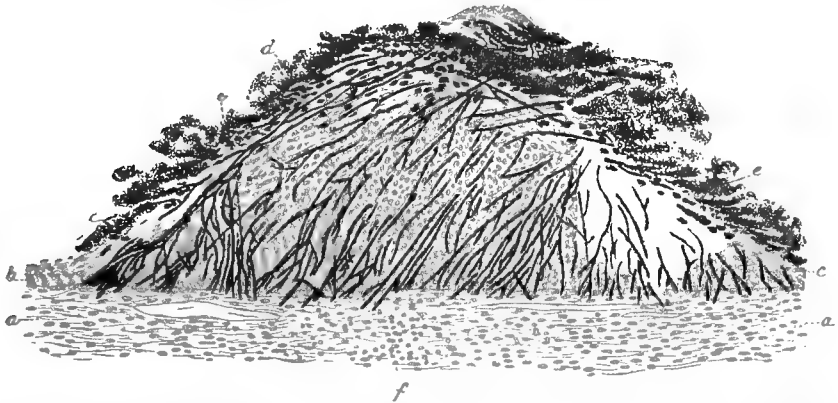
Fig. 469.—Section through a thrush-covered œsophagus of a small child (alcohol, carmine, Gram's). *a,* Connective tissue; *b,* normal epithelium; *c,* swollen and desquamated epithelium infiltrated with fungus-threads; *d,* epithelium infiltrated with cells; *e.* cocci and bacilli; *f,* cellular focus in the connective tissue. × 95.

reported a case in which a mould-fungus was conveyed from an intestinal ulcer to the brain and lung. Schmorl and Heubner have described thrush-metastases in the kidneys.

Moreover, **growths of moulds in the lungs** are not always confined to dead material or to the cavity of the bronchus, but it occasionally happens that they penetrate the living respiratory parenchyma, forming small white or yellowish, nodular masses, in which the lung tissue is necrotic, while in the neighborhood there is inflammatory infiltration. In the injured *cornea* they may likewise penetrate and cause necrosis and inflammation.

Local **colonizations of moulds** cause more or less marked irritation of the surrounding tissues, and give rise to *degeneration* (Fig. 469, *c*) and *inflammation.* Such changes may be observed in mycosis of the lung, and of the intestine (*c, d, f*) and ear. Invading the lungs they form hyphæ which resemble the granules of actinomycosis, and are surrounded by collections of cells. Their action, however, is limited; they produce no substances which are injurious to the organism as a whole, or which cause symptoms of poisoning. The finding of moulds in abscesses of the subcutaneous tissues and internal organs is probably due to the fact that,

with the bacteria of suppuration, moulds get into the tissues, as well as into the circulation. Generalization of mould-fungi does not occur in these cases; the development of the mould is confined to the place of metastasis.

The moulds which are saprophytic, or, to a limited extent, parasitic in man, belong to the **Mucor, Aspergillus, and Eurotium** genera. From the ear various species have been obtained: *Aspergillus fumigatus, Aspergillus flavus* or *flavescens, Aspergillus niger* or *nigricans, Aspergillus nidulans, Eurotium malignum, Mucor corymbifer,* and *Trichothecium roseum;* so far as known, these are the same species which occasionally occur in the respiratory tract.

FIG. 470.—Mucor corymbifer in fructification (culture upon glass-slide). *a,* Aerial hyphæ; *b,* mycelia lying within the nutrient gelatin; *c,* branching fruit-bearers; *d,* sporangia. × 100.

In the mucors there appear special *fruit-bearers* (Fig. 470, *c*), which according to the species are single or branched, and on the ends of which are knob-like swellings from which the *sporangia* (*d*)—that is, spherical vesicles filled with conidia-spores — grow.

Mucor corymbifer, for example, forms branched fruit-bearers (Fig. 470, *c*). The sporangia (*d*) on the ends possess a smooth membrane and enclose at the time of ripening yellowish conidia-spores.

FIG. 471.—Hyphæ with conidia-bearers of *Aspergillus fumigatus. a,* Fruit-head in optical cross-section; *b,* fruit-head seen from above. × 275.

The aspergilli form *conidia-bearers,* which swell spherically above, and then produce numerous *sterigmata* — that is, cone-like outgrowths, radially arranged, thickly crowded, and sprouting from the upper half of the sphere. From each sterigma a *chain of conidia* is later constricted off (Fig. 471, *a, b*).

The *botanical position of the fungus of thrush* is still unsettled. Formerly it was called **Oïdium albicans,** and classed with the genus Oïdium, which occurs in different species in the form of filmy coatings on organic substances. When cultivated from conidia is produces hyphæ which become joined and develop conidia through transverse division of the threads, but form no peculiar fruit-bearers.

According to Rees, Grawitz, Kehrer, the thrush-fungus grows by budding and by the production of mycelia and conidia, which in turn

produce at their ends, by a process of constriction, new conidia, in a manner similar to that which takes place in the forms of mycoderma belonging to the yeast-fungi. Consequently this fungus should be designated *Mycoderma albicans*. Linossier and Roux are, however, of the opinion that the thrush-fungus does not belong to the saccharomycetes. Caò, who has investigated numerous *varieties of oïdium*, regards the oïdia as a well-defined class of fungi standing between the blastomycetes and the hyphomycetes, which they approach through the production of mycelia.

According to Plaut the thrush-fungus is identical with a mould, *Monilia candida,* which occurs frequently in nature. Kehrer suspects that it is one of the higher moulds that has become degenerate through parasitism.

According to *Neumayer* all *varieties of yeasts* are resistant to the digestive juices, and may pass through the human intestinal tract without being killed. They exert an influence on the intestinal canal only when fermentable substances are introduced, whereby at the high temperature of the body abnormal products of fermentation are produced having an irritating action on the intestinal tract.

Busse found (1894) great numbers of yeast-cells developing in the diseased areas present in a woman, thirty-one years of age, who died from multiple inflammations of the bones, skin, lungs, kidneys, and spleen, partly tumor-like and partly abscess-forming. According to his findings it may be regarded as certain that the yeast was the cause of the disease. The yeast could be easily cultivated on suitable media. Mice were particularly susceptible to inoculation, dying in from four to eighty-three days after the injection. At death the yeast-cells were found to have increased both at the point of inoculation, and in the internal organs. Proliferation of tissue occurred only after long duration of the infection.

Buschke found yeasts in multiple ulcers of head and neck, arising from acne-like lesions. *Gilchrist* and *Stokes* found yeasts in a lupus-like affection of the skin. *Löwenbach* and *Oppenheim* found a yeast in the skin of the nose showing nodules and scar-tissue.

In 1896 *Gilchrist* described a progressive affection of the skin characterized by epithelial hyperplasia, miliary abscesses, and infiltration of the cutis. In the abscesses doubly-contoured, refractive, round and oval bodies were found. They varied in size from 10–20 μ and presented buds of varying size. To this organism the name of *Blastomyces dermatitidis* was given, and the skin condition was called *blastomycetic dermatitis.* Many cases of this kind have since been reported, the majority of them by Chicago observers. In some of the cases a fatal generalized infection has been seen. The organisms cultivated from the cases fall into three groups: 1, blastomycetoid; 2, oidium-like; and 3, a hyphomycetoid group. According to *Ricketts* they may be included in a common genus, *Oidium,* and he has proposed the term *oidiomycosis* for the various lesions produced by these organisms. At the present time the exact botanical classification of the latter is not possible.

Under the designation of *coccidioidal granuloma* there has been described a condition closely resembling oidiomycosis, but apparently differing from it in certain clinical characteristics and in the nature of the organisms found in the lesions. It runs a more severe and progressive course than the latter condition, and generalized infection is the rule. The organism multiplies by endogenous sporulation instead of by budding. *Ophüls* would class it with the oidia under the name of *Oidium coccidioides.* The lesions produced by it resemble tubercles closely in the majority of cases, and clinically the disease has been mistaken for tuberculosis. Of 35 cases collated by Hektoen and by Brown up to 1907, 34 originated in California, many of them in the San Joaquin Valley, chiefly in men engaged in railway construction. The disease occurs (*a*) as a primary pulmonary affection with or without cutaneous lesions, (*b*) as a primary lesion of the skin, and (*c*) as a generalized process following either primary cutaneous or pulmonary infection. Clinically, the cutaneous lesions may resemble those of glanders. Moreover, injection of the pus into male guinea-pigs may be followed by changes in the scrotum and testicles resembling those produced by glanders bacilli.

Sanfelice experimented with yeasts from fruit-juices, and found among these one pathogenic for guinea-pigs (*Saccharomyces neoformans*) and one pathogenic for chickens and dogs (*Saccharomyces lithogenes*). *Curtis* found, in multiple proliferations of the skin resembling myxosarcoma, yeast-cells which were pathogenic for mice, rats, and dogs. *Cohn,* who experimented with the yeast described by *Klein,* found that its inoculation into the peritoneal cavity of mice caused death through the formation of great yeast-tumors. The intravenous injection of larger animals led to severe disturbances of brain and spinal cord, associated with inflammation of the mucous membranes, particularly of the conjunctiva.

Sanfelice, Corselli, Frisco, Rancali, Binaghi, Leopold, and others believe that blastomycetes may be the cause of true tumors, sarcoma and carcinoma; but true tumors have never yet been produced experimentally by inoculations of yeast-cells or by injections of the same into the blood. Only suppurations and inflammatory tissue-proliferations have been produced by such experiments; and the finding of yeast-like structures in true tumors, even if part of these were true yeast-cells, does not permit the conclusion that tumors are caused by yeasts.

According to investigations by *Koch, Löffler, Lichtheim, Hückel,* and *Lindt,* the conidia of *Aspergillus fumigatus, A. flavescens, A. nidulans, Eurotium malignum, Mucor rhizopodiformis, M. corymbifer, M. pusillus,* and *M. ramosus,* grow at the body-temperature, and, when introduced into the blood-current of animals, grow into the tissues and form hyphæ, although there is no new-formation of conidia, and consequently no progressive infection of the animal extending beyond the area within which the spores have been introduced. Conidia of *Mucor rhizopodiformis* and *M. corymbifer* grow, when introduced into the blood-stream of rabbits, chiefly in the kidneys and the lympathic apparatus of the intestines, where they cause hæmorrhagic inflammation. According to *Caò,* there are different species of oidia which, when injected into rabbits, cause inflammations, abscesses, or proliferations of granulation tissue; many produce also a toxic action on the organism.

According to *Ceni, Aspergillus fumigatus* which grows at summer temperature produces poisons in its conidia. One of these can be extracted with alcohol and causes tetanic convulsions in experimental animals. It is possible that the aspergillus growing on corn plays a rôle in the etiology of pellagra.

Aspergillus mycoses of the respiratory tract are not rare in animals, especially in birds, and the proliferating mycelia cause tissue-necrosis and inflammation. According to *Chantemesse, Aspergillus fumigatus* causes in pigeons diseased conditions of the mouth, lungs, liver, and kidney, that of the first two organs resembling diphtheria, that of the latter two closely resembling tuberculosis. It may, therefore, be designated *pseudotuberculosis aspergillina.* According to *Potain,* the infection may be transmitted to man and give rise to ulcerative diseases of the lung.

Eurotium and *Aspergillus,* according to *Siebenmann,* are two different families, having, however, a close resemblance to each other, in that the mycelia and conidia are similarly formed. The essential differences between the two lie in the fact that *Eurotium* produces perithecia in the form of shining, light-yellow or sulphur-yellow, translucent bodies the size of a grain of sand, delicate and easily crushed, and which ultimately develop into spores capable of germination; while the true *Aspergillus* forms hard, woody sclerotia usually embedded in a thick, white matted mass of mycelia. The development of these takes place in two periods. The second part of the development occurs only when the sclerotium finds lodgment upon a moist substratum.

Aspergillus flavus of *Brefeld* (*Eurotium Aspergillus flavus* of *de Bary*) forms golden yellow, green, and brown growths; round, yellow, olive-green, or brown fruit-heads; round, rarely oval, sulphur yellow to brown conidia with minute warts on the surface; diameter 5–7 μ. *Aspergillus fumigatus* of *Fresen* (*Aspergillus nigrescens* of *Robin*) forms green, bluish, or gray growths; the fruit-heads are long, in shape resembling an inverted cone; conidia, round, rarely oval, smooth, mostly clear and colorless; diameter 2.5–3 μ. *Aspergillus niger* of *Van Tieghen* (*Eurotium Aspergillus niger* of *de Bary*) forms dark chocolate-brown growths; conidia are round, brownish-black, or grayish-brown when ripe; surface smooth or warty; diameter 3.6–5 μ.

Aspergillus can develop upon the injured cornea and give rise to purulent inflammation. *Leber* (*Graefe's Arch.,* xxv.) cultivated it upon the cornea and in the anterior chamber of the eye of the rabbit. Finally, *Aspergillus* also appears in the pelves of the kidneys. *Babes* (*Biol. Centralbl.,* ii.) found the conidia and hyphæ of a mould in ulcers of the skin which were covered by scabs, and gave to it the name of *Oidium subtile cutis.*

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§ 182. **Thread-fungi** are to be regarded as the **exciting cause of** certain **affections of the skin,** as *favus, herpes tonsurans, pityriasis versicolor, erythrasma.* In all of these diseases the epithelial parts of the skin contain colonies of hyphæ and conidia.

The **fungus of favus** (Fig. 467) is usually called **Achorion Schönleini** (discovered by Schönlein in 1839).

Favus (tinea favosa, scald-head) affects the hairy portions of the head, more rarely other regions, for example, the substance of the nails. It is characterized by the formation of discs (*favus scutula*), varying in size from a lentil to that of a five-cent piece, of surphur-yellow color, and indented or pierced by a hair. In an abortive course it may merely form scales similar to those of herpes.

According to Kaposi, the favus scutulum originates as a small, punctiform, yellow focus lying under the epidermis and penetrated by a hair. This grows in a few weeks to the size of a lentil and then forms a sulphur-yellow, indented disc showing through the upper layers of the skin. The scutulum consists of hyphæ and conidia spores, and lies in a cup-shaped depression of the skin, beneath the horny layer, which is drawn away above it. If the mass be removed during life, the cavity shows a red moist surface. The favus itself forms a white, crumbling mass which is easily disintegrated in water.

If the scutula are not removed, they join to form larger masses. When the epidermis is desquamated the favus-mass becomes exposed and dries into a yellowish-white, mortar-like material. The hairs appear

lustreless, as if covered with dust, and are easily pulled out, since the mycelia and conidia of the fungus penetrate into the hair-shaft and hair-bulb, as well as into the sheath of the hair-root.

Through the growth of the fungus-masses the hairs may not only be shed, but the papillæ become atrophic. At the same time there is produced in the neighborhood of the hair-follicle more or less intense inflammation which may take on an eczematous character.

The development of achorion in the nails (*onychomycosis favosa*) gives rise to sulphur-yellow deposits or uniform thickenings of the parenchyma of the nails with simultaneous loosening and cheesy disintegration.

Trichophyton tonsurans, the fungus of *herpes tonsurans* (*" barber's itch," " ringworm "*), consists of long narrow threads, branching but little, and with few conidia. It forms no scutulous masses, but penetrates easily into the hair-shaft, and makes the hairs brittle. It shows certain differences of growth, according to whether the herpes develops on hairy surfaces or on areas devoid of hairs.

Herpes or *Trichophytosis tonsurans capillitii* forms bare discs varying in size from a five-cent piece to that of a dollar. Those spots in which the hairs are broken off short resemble places in which the hair has been badly shaven. The surface is smooth or covered with scales, and somewhat reddened at the border of the disc. If the fungus-threads penetrate the hair-follicles, pustules and scabs are formed. Such discs may appear in many places, and may increase in size until healing finally takes place.

FIG. 472.—Culture of *Trichophyton tonsurans.* *a,* Branching threads with long joints which have delicate walls; *b,* threads with thick-walled, short segments, some of them being spherical. × 270.

On places devoid of hairs the herpes forms vesicles (*Herpes tonsurans vesiculosus*), and red scaly spots, discs, and circles (*Herpes tonsurans squamosus*). At times red spots appear in numerous places; these quickly spread, and as rapidly heal. The fungus is found between the uppermost layers of the epidermis, beneath the stratum corneum (Kaposi).

If trichophyton develops in the nail, the nail becomes cloudy, scales off, and is easily broken — a condition designated *onychomycosis trichophytina.*

Sycosis parasitaria arises through development of the fungus accompanied by severe inflammation of the hairy parts of the skin, leading to infiltration and suppuration — that is, to the formation of pustules, abscesses, and papillary proliferations. According to Kaposi and others **eczema marginatum** is also caused by trichophyton tonsurans. The condition occurs in those regions where two surfaces of skin come into

contact with each other and are macerated by sweat; and is characterized by the formation of vesicles, pustules, and scabs, which are situated at the periphery of a pigmented surface.

Microsporon furfur, the fungus of **pityriasis** or **mycosis versicolor** or **dermatomycosis furfuracea,** likewise occurs in the form of hyphæ and conidia, which are somewhat smaller than those of other skin-fungi. The pathological changes produced by this fungus are characterized by the formation of pale yellow or yellowish-brown to dark-brown and brownish-red spots, varying in size from a lentil to that of the hand, sometimes smooth and shining, at other times dull and exfoliating, and of irregular shape. They may be spread uniformly over large areas of skin; and are found chiefly on the trunk, neck, and flexor surfaces of the extremities, but never on the hands, feet, or face.

Microsporon minutissium is the name given to a thread-fungus, which is found in the skin affection known as **erythrasma.** The disease is characterized by the formation, on the inner side of the thigh, of brown or reddish-brown patches, which are only slightly scaly, and may be as large as the palm of the hand. The fungus is found in the epidermis, and is smaller than that of pityriasis.

The thread-fungi occurring in the diseased areas of the skin may be cultivated on proper media (agar-agar, agar-glycerin, gelatin, potatoes, blood-serum, etc.), and on such the conidia develop into single and branching threads, which become jointed (Fig. 472, *a*), and form chains of short cells (*b*). Club-like formations which frequently appear on the ends of the threads in cultures, are regarded by Quincke and Elsenberg as imperfect sporangia. The botanical position of these fungi is not yet determined; and nothing is known with certainty concerning their distribution outside the human and animal body.

According to *Quincke,* three forms of fungi occur in favus-masses, two of these being varieties of one species of fungus. *Elsenberg* found only two, which he regards as varieties of the same species. *Pick, Plaut,* and *Biro* believe in the eitological unity of favus.

Sabouraud advances the view that the fungi causing trichophytosis represent different species, all of which belong to the genus *Botrytis. Krösing* distinguishes three groups of trichophyton-fungi according to the different appearances of the cultures on potato, and emphasizes, moreover, the differences in their organs of generation and fructification. *Rosenbach,* who has studied the moulds occurring in deep suppurating inflammations of the skin, differentiates several trichophyton-fungi as the cause of these affections.

According to *Spietschka,* the *Microsporon furfur* may be cultivated from the scales of the skin, and in cultures can be well differentiated from other pathogenic thread-fungi. Through inoculation of the fungus typical mycosis may be produced in man.

From the great number of recent investigations by various writers it is impossible to deduce anything definite concerning the number of kinds of favus- and trichophyton-fungi. It is, however, evident from these investigations that the nature of the nutrient medium influences the character of the growth (*Sabouraud, Waelsch*), and the difference in findings is to be referred in great measure to differences in the nutrient media on which the moulds were grown.

Inoculations with fungi grown in cultures into the skin of human beings, rabbits, mice, etc., which were made by *Grawitz, Boer, Münnich,* and others, gave partly negative, partly positive results. According to *Plaut,* the inoculations never give positive results when spore-formation has taken place in the cultures.

Von Hebra has described (*Wiener med. Blätter,* 1881: "Die krankh. Veränd. d. Haut," Braunschweig, 1881) as *dermatomycosis diffusa flexorum,* a peculiar itching dermatosis, which occurs on the elbow and bend of the knee and is thought to be caused by fungi, which are like those of *pityriasis versicolor.*

According to the investigations by *Wehmer*, the cause of the skin eruption known as *tokelau* which occurs in various South Sea Islands (Fiji, Samoa, and Solomon) and which is characterized by the formation of scaly rings, is an Aspergillus.

Favus and *herpes tonsurans* occur in **domestic animals,** as well as in *mice* and *rats* (cf. *Friedeberger* and *Fröhner,* "Lehr. d. spec. Pathologie der Hausthiere"). *Waelsch* inoculated human individuals with favus fungi, which he had cultivated from mice affected with favus, and obtained typical favus scutularis.

Intravenous injections of favus-fungi into rabbits (*Bukovsky*) produced in the lungs of these animals a form of pseudotuberculosis; and cellular nodules are found in which fungus threads have developed in a manner suggesting the lesions of actinomycosis. After a time the fungi die.

In **Invertebrate animals** there not infrequently occur diseases produced by mycelium-fungi. Thus *Botrytis Bassiani* causes the so-called muscardine in silk-worms; *Cordyceps militaris* destroys the injurious pine-spider *Gastropachia pini; Tarichium megaspermum,* a black-colored fungus, kills the destructive earth-cater-pillar *Agrotis segetum.* Fungi belonging to the genus *Empusa* attack the caterpil-lars of the cabbage-butterfly (*Empusa radicans*), and the house-fly (*Empusa mus-cæ*), their mycelia growing through the caterpillar and finally killing it. *Achyla prolifera,* according to *Harz* (*Jahresber. d. Münchener Thierarzneischule,* 1882–83), grows through the musculature of crayfish, and is the cause of the crayfish pest.

CHAPTER XII.

The Animal Parasites and the Diseases Produced by Them.

I. Protozoa.

§ 183. Of the **Protozoa** occurring as parasites in man, only a small number was known up to a few years ago; and even the known forms possessed but slight significance, since there could be ascribed to them no marked influence on the tissues. Through the investigations of the last few years, however, different forms have been recognized as the cause of morbid processes; and it is quite possible that there are still other protozoa capable of exciting pathological changes in the human body. The forms already recognized are representatives of all four classes of protozoa.

Of the **Rhizopoda** there occur in the intestine three amœbæ, known as *Amœba coli vulgaris, Amœba coli mitis,* and *Amœba dysenteriæ.* The Amœba dysenteriæ is distinguishable from the other two, while the Amœba coli vulgaris and the Amœba coli mitis resemble each other closely, and may be identical.

FIG. 473.—*Amœba coli mitis.* (After Roos.) *a,* Free motile amœbæ; *b,* encysted amœbæ. × 590.

The **Amœba coli vulgaris** is a harmless parasite which is not infrequently present in the intestine (Roos, Kruse, Pasquale). The **Amœba coli mitis** was observed by Roos and Quincke in cases of chronic enteritis in patients who had always lived in North Germany.

The Amœba coli mitis consists, according to Roos, of a protoplasmic cell-body, from 28–30 μ in diameter, (in the spherical condition). It exhibits slow movements, and frequently encloses foreign bodies, for example, bacteria and food remains (Fig. 473, *a*). Besides the motile form, there occur, according to Roos, encysted spherical forms which are surrounded by a double-contoured membrane, and enclose clear, round vesicles in their interior (*b*). When fed to animals (cats) no pathogenic properties are disclosed.

FIG. 474.—*Amoeba dysenteriae sive Amoeba coli felis.* (After Roos.) *a,* Amœbæ without inclusions; *b,* amœbæ containing blood; *c,* amœbæ with large vacuoles in their protoplasm; *d,* young forms; *e,* encysted forms. × 665.

The **Amœba dysenteriæ** (identical with the Amœba coli described by Loesch) has a diameter, according to Roos, of from 15–25 μ, but according to Kruse and Pasquale, from 10–50 μ. In the cell-body there may be recognized a homogeneous ectoplasm and a granular entoplasm, the arrangement of which varies according to the form of the animal (Fig.

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474, *a*). By staining, a nucleus becomes visible in the cell. The cells are capable of active movement, and thereby assume varied shapes (*d*). They often contain foreign bodies, particularly red blood-cells or remains of such (*b*), or are studded with clear vacuoles (*c*). According to Roos, they may also become encysted (*e*).

According to Koch, Kartulis, Kruse, and Pasquale, they are invariably present in the dysentery prevailing in Egypt, and are usually demonstrable in the dejecta. They have also been observed in dysentery in Russia, in America, in Germany, and in Austria. According to investigations by Kartulis, Councilman, Lafleur, Kovacs, Roos, Kruse, Pasquale, and others, it cannot be doubted that they are of significance in the origin of certain forms of dysentery. It is only questionable whether they alone, or with the aid of changes produced by bacteria, are able to bring about pathological alterations. In support of the latter theory is the fact that, when present in the tisues, they are always accompanied by bacteria.

Amœbic dysentery is characterized by the occurrence of a hæmorrhagic catarrh, and by the formation of circumscribed ulcers with undermined edges. The amœbæ increase not only in the intestinal mucosa, but penetrate into the mucosa and submucosa, and form large colonies, in the region of which the tissue undergoes necrosis without the formation of any large amount of exudate. By rupture of the submucosal foci through the mucosa there are formed ulcers with undermined edges, which, gradually increasing in size, may attain large dimensions.

If *abscesses of the liver* arise during the course of amœbic dysentery, these may contain the amœbæ in addition to bacteria; it may be assumed that the former also take part in destruction of the liver tissue.

The *amœbæ of dysentery are pathogenic for cats,* and, when fed to them or when introduced into the rectum of the animal, cause a rapidly progressive, often fatal dysentery, which is similar in all respects to amœbic dysentery in man. The amœbæ also penetrate into the mucosa and submucosa of these animals.

Von Leyden and *Schaudinn* ("Leydenia gemmipara," *Sitzber. d. K. Akad. d. Wiss.,* Berlin, 1896), found, in the fluid of two cases of ascites occurring in malignant disease of the abdomen, an amœba which consisted of colorless gelatinous cells, which put out pseudopodia, and showed a hyaline entoplasm and a granular ectoplasm. They were found chiefly in groups.

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§ 184. A large number of species of the **Flagellates** (sub-class of the *Mastigophora*) occur in man, mammals, and birds, most frequently as parasites of the body-passages accessible from without, but occurring also in the blood.

Cercomonas, a small flagellate (Fig. 475) with a flagellum on the anterior end and a long-drawn-out posterior extremity, was observed by Kannenberg and Streng in gangrenous foci of the lung.

FIG. 475.—*Cercomonas intestinalis.* (After Davaine.)
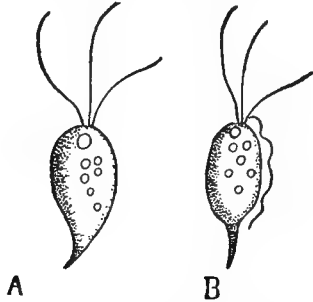
FIG. 476.—*Trichomonas hominis,* after Grassi (from Doflein).
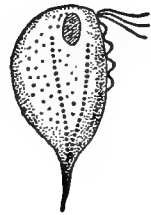
FIG. 477.—*Trichomonas vaginalis* (from Doflein).

Trichomonas (*Cercomonas intestinalis,* Lambl; *Trichomonas intestinalis,* Leuckart; *Monocercomonas hominis,* Grassi) is a pear-shaped flagellate, 4–10 μ long, with three flagella on the anterior end (Fig. 476),

Trichomonas hominis occurs in the small intestine of man. It appears to be a harmless inhabitant of alkaline intestinal contents.

Trichomonas vaginalis is a flagellate similar to *Trichomonas hominis* (Fig. 477), and is often found in the human vagina. According to Miura, Marchand, and Dock, it may occur in the human urinary bladder.

Lamblia intestinalis (*Megastoma entericum,* Grassi; *Megastoma intestinalis,* Blanchard; *Cercomonas intestinalis,* Lambl; *Hexamitus duodenalis,* Davaine) is a turnip-shaped animal, having an indentation on the ventral surface (Fig. 478, *A, B*). It is about 10–16 μ long, and is found especially in the upper part of the small intestine, and has been observed in man, mice, dogs, cats, sheep, and rabbits. The parasite clings tightly to the epithelium of the intestine, but no pathological changes can be demonstrated in the underlying tissue.

§ 185. Of the **Flagellates** that occur as **blood-parasites of man** the form known as **Spirochæte obermeieri** has been known for some time, but formerly was classed with the spiral varieties of bacteria (spirilla). The investigations of Schaudinn, however, make it probable that the spirochætes are to be added to the protozoa.
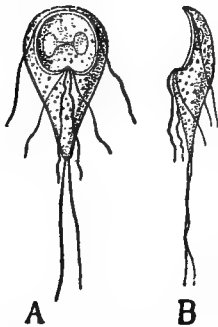
FIG. 478.—*Lamblia intestinalis* (after Grassi and Schewiakoff). *A,* View from ventral surface; *B,* view from the left side.

Schaudinn's conclusions are not universally accepted. According to *Novy,* **Spirillum obermeieri** belongs to the bacteria and not to the protozoa, and he believes that the majority, if not all, of the spirochætes will be returned to their former place among the bacteria. *Sp. duttoni* and *Sp. gallinarum* have both been shown to be non-protozoal in nature.

The **Spirochæte obermeieri** (Fig. 479) is found constantly in the blood of patients suffering from **relapsing fever** during the attacks of fever, and the multiplication of these organisms in the body is the cause of the disease.

The spirochæte is 16–40 μ long, and possesses numerous spiral turns. In a fresh drop of blood it shows active motion. The subcutaneous inocu-lation into apes of blood containing the spirochæte is followed after several days by an attack of fever, and the spirochæte is found in the blood during the febrile stage. The life history of the Spirochæte obermeieri is not known, but it may be similar to that of the spirochætes occurring in the blood of birds as studied by Schaudinn (see below). Accord-ing to autopsy-findings in man, the spleen is swollen and contains numerous yellow foci of degeneration, and anæmic infarcts.

FIG. 479.—*Spirochaete Ober-meieri* from the blood of an indi-vidual ill with relapsing fever. After a dried preparation stained with methylene blue. × 475.

According to investigations by Nikiforoff, the histological examination of the spleen shows extensive cell-necrosis and cell-degeneration (Fig. 480, *c*), as well as deposits of fibrin in the veins of the pulp, and proliferative proc-esses in the pulp-cells. Further, numerous large pulp-cells (*f*) enclose red and white blood-cells or the remains of such. Finally, numerous spirilla are found, especially in regions which are not wholly necrosed but contain degenerate and necrotic cells, free (*a*), and enclosed in

FIG. 480.—Portion of tissue and isolated cells from a splenic follicle with partial necrosis, in relapsing fever. (After Nikiforoff.) (Potassium bichromate and sublimate, methylene-blue.) *a*, Free spirilla; *b*, lymphocytes with spirilla; *c*, non-nucleated lymphocytes; *d*, large, *e*, small mononuclear pulp-cells; *f*, phagocytes enclosing leucocytes and red blood cells and their remains; *g*, free red blood-cells. × about 600.

leucocytes (*b*), partly well-preserved, and partly beginning to show disintegration.

According to Karlinski and Schaudinn, the infection is probably transmitted by bed-bugs.

Spirochætes have been observed also in birds, owls (Schaudinn), geese (Sacharoff, Gabritschewsky), and fowls (Marchaux, Salimbeni, Levaditi), and may cause epidemics in which great numbers of animals perish.

The **life-history of the Spirochætes** classed with the bacteria was not known until recently. Through the investigations of *Laveran* and *Schaudinn* it was first determined that in their life-cycle there occurs an *alternation of generation and of host*. *Schaudinn* carried out his studies on the spirochætes found in the small owl (*Athene noctua*), which he named *Spirochæta ziemanni* (called by *Laveran* the *Hæmamœba ziemanni*). As a result of his investigations he believed that he had demonstrated the transmission of this spirochæte from the owl to the mosquito, *Culex pipiens,* in the intestine of which it passed certain stages of development, as described in the following paragraphs.

Within the owl there develop male and female individuals, the microgametocytes and the macrogametes. Copulation takes place in the intestine of the mosquito. From the fertilized macrogamete there develops an oökinete which produces in the intestine of the mosquito an enormous number of trypanosome-like offspring. These become transformed into true spirochætes, spread through the body of the mosquito, increase by logitudinal division, and wander into the œsophagus, whence, in the act of biting, they again pass into the blood of the owl. After an asexual period of multiplication in the form of spirochætes they again form gametes or sexual individuals in the blood of the owl. As a result of their distribution through the body of the mosquito the spirochætes pass into the ovaries of the latter and are transmitted to the next generation.

The fertilization in the intestine of the mosquito follows ripening of the macrogametes (female cells) and the formation of microgametes (spermatozoa) from the microgametocytes. The oökinete resulting from the fertilization of a macrogamete is a worm-like body rolled up into a complicated skein. Through grouping of the protoplasmic masses around the individual nuclei there are formed small trypanosome-like individuals having a characteristic flagellum-apparatus. Further, there may be developed both male and female individuals. The female forms are larger than the indifferent forms, their plasma is dark, the nucleus and blepharoplast relatively small, and the margin of the undulating membrane is not continued to form a flagellum. The males are small and scarcely recognizable.

Through continued division the indifferent spirochætes in the intestine of the mosquito also become very small, so that single individuals can barely be made out.

Within the blood of the owl the spirochætes become parasites of the hæmoglobin-containing erythroblasts, in that they attach themselves to these by their posterior extremities. This is seen particularly in the bone-marrow and also in the spleen. After a certain time they form in the blood macrogametes and microgametes, which, on gaining entrance into the mosquito, again form new generations in the manner described. The *macrogametes* can also produce *new generations* in the blood without fertilization (parthenogenesis) and thereby *cause relapses.*

The above-given life-cycle of the spirochætes according to *Schaudinn* falls to the ground in the light of *Novy's* studies. The latter has shown that the *Spirochæte ziemanni* is not a spirochæte, but a trypanosome, and has no connection with the intracellular parasites of the owl's blood. Further, *Novy* regards *Sp. obermeieri* as belonging to the bacteria, basing his view on his inability to demonstrate in the organism a nucleus, blepharoplast, undulating membrane, or flagellum of the protozoan type. On the other hand the spirilla of relapsing fever possess whips having all the characteristics of those of bacteria, divide transversely, multiply rapidly, resist changes in osmotic tension, show a greater resistance to heat than do the trypanosomes, excite the production of immune and germicidal bodies, and do not exhibit the aërotropism shown by trypanosomes.

In *relapsing fever we have most probably to deal with a group of closely related organisms* (*Novy*), which, while they may in one sense be regarded as distinct species, are derived from one stem. Five distinct strains of spirilla causing relapsing fever have been discovered: *Spir. obermeieri, Spir. novyi, Spir. kochi, Spir. duttoni,* and *Spir. carteri.* These differ from each other in the duration and severity of the initial attack, the frequency and intensity of relapses, and in the mortality following injection of a uniform dose of 0.25 c.c of spirillar blood. The relapse is probably due to the survival of a few individuals that are more or less immune, so that a serum-fast strain develops. This in turn calls out a new anti-body. If this is less active or more unstable, or more readily eliminated, the relapses continue

If *Schaudinn's* views on the protozoan nature of the organism found in syphilis (*Spir. pallida, Treponema pallidum*) are correct, that organism should then be classed with the protozoa. At the present time this question cannot be regarded as settled, but it is most probable that the organism is of bacterial nature and should be classed, along with the spirochætes of relapsing fever, with the spiral forms of bacteria (*spirilla*). (See Syphilis.)

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§ 186. The genus **Trypanosoma** forms a second class of **blood-parasites** belonging to the **Flagellata,** found in man, mammals, and birds, and also in cold-blooded animals. Most authors place all the parasites of this class in the genus trypanosoma and distinguish different species. Doflein
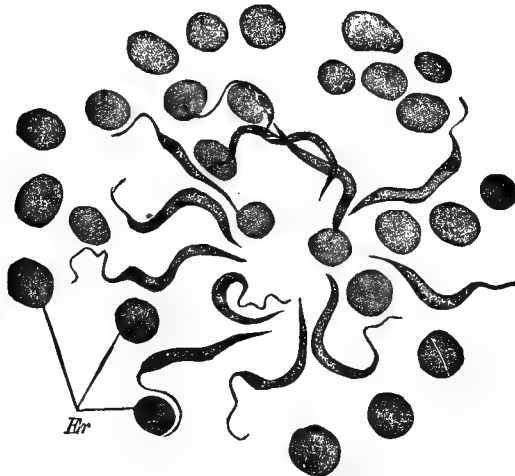
Fig. 481.—*Trypanosoma (herpetosoma) lewisi* in the blood of the rat. (From **Doflein** after Rabinowitsch and Kempner.) *Er,* Erythrocytes.

divides them according to the character of the flagella into three subgenera: *Trypanosoma, Trypanomonas,* and *Herpetosoma.* Van Wasielewski classes only the blood-parasites of the frogs and fish with the trypanosomes, and would apply the name *Herpetomonas,* given by Kent, to the trypanosomes found in mammals.

Trypanosoma lewisi (*Herpetomonas, Trypanomonas, Trichomonas, Hœmatomonas*) is a common parasite of rats. It is 8–30 μ long and 3–8 μ broad (Fig. 481), consists of a nucleated granular entoplasm and a delicate hyaline ectoplasm or periplastem, the latter forming an undulating membrane (Fig. 482, *c*) and a flagellum (*d*) which arises in the beak-like posterior end from a rod-like body and extends anteriorly along the edge of the undulating membrane.

The rod-shaped body (*b*) is designated micronucleus, or nucleolus, or centrosome, or blepharoplast. It has the significance of a nucleus and arises from the chief nucleus.

The trypanosome infection occurs extensively among rats of many regions. In other animals these trypanosomes do not appear to develop. The infected rats are apparently healthy, yet epidemics occur in which great numbers of them die. Intraperitoneal inoculations of rats are followed by multiplication of the trypanosomes, in the abdominal cavity and in the blood. According to Rabinowitsch and Kempner reproduction
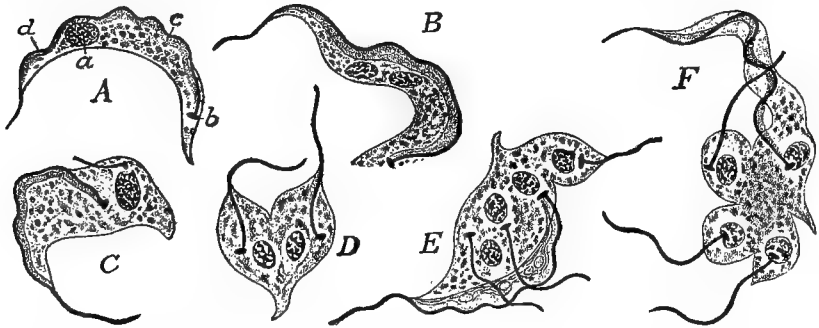
Fig. 482.—*Trypanosoma (herpetomonas)* lewisi, in different stages of development. (After A. von Wasielewski.) *A*, Fully developed parasite with nucleus (*a*), rod-shaped body (*b*), undulating membrane (*c*), and flagellum (*d*); *B*, parasite with two nuclei and one rod-shaped body; *C*, parasite with one nucleus and two rod-shaped bodies; *D*, division into two parasites; *E*, parasite with four nuclei and four flagella; *F*, daughter-individuals still united into a colony. × 1,500.

takes place by longitudinal and transverse division of flagellated individuals, and through the segmentation of large non-flagellated forms in which cell-division is initiated by division of the nucleus, designated as the chromatin framework, while new nucleoli are snared off from the chromatin mass. According to von Wasielewski the chief nucleus (*B*) sometimes first divides, at another time the rod-shaped root of the flagellum or the blepharoplast (*C*); the cells sometimes divide with two nuclei (*D*), and sometimes after the formation of several nuclei and flagellum-roots (*E*, *F*), so that the resulting dividing flagellates remain for some time united in colonies. The infection of rats occurs probably through the medium of fleas and lice.

Trypanosoma brucei, Plimmer and Bradford, is similar to *Tr. lewisi,* only the body is somewhat broader and the posterior end somewhat blunter. It is the cause of **Nagana** or the **tsetse-fly disease** of cattle, horses, antelopes, buffalo, donkeys, dogs, sheep, and goats, occurring in Southern and Southeastern Africa, which is transmitted through the *tsetse-fly* (*Glossina morsitans*). The number of parasites in the blood may be great; infected animals suffer from fever and become anæmic;

œdema develops in different parts of their bodies; there is conjunctivitis and the spleen is swollen. The period of incubation is not more than nine days. The infected animals die after one and one-half to eight months.

It is probable that the disease known as **Surra,** occurring endemically in horses, mules, camels, buffalo, cattle, and elephants in Dutch India, Indochina, and the Philippines, and which is transmitted by gad-flies, is due to this trypanosome. It is likewise regarded as the cause of the trypanosome disease of horses and donkeys known as the coitus-disease or **dourine** occurring in Algiers, Southern France, Sumatra, Novarra, and the Pyrenees, and which is spread by coitus, and is inoculable into rabbits, rats, and dogs. Many authors regard the parasites found in these diseases as representing different species, giving to the first the name of *Trypanosoma evansi* and to the latter that of *Tr. equiperdum.* A variety of trypanosome found in Central South America and which causes the disease of horses known as *mal de caderas* is designated *Tr. equinum.* It is assumed that *Stomoxys calcitrans* acts as the agent of transmission of the parasite.

A variety of trypanosome known as *Tr. theileri* is found in cattle in South Africa and is inoculable only into cattle.

The occurrence of **trypanosomes in man** was first observed by Nepveu (1898). The investigations of Dutton, Todd, Boyce, Ross, Sherrington, Bruce, Castellani, Manson, Daniels, Laveran, etc., have shown that trypanosome diseases also occur in man. The **sleeping-sickness of the negro** is now known to be due to trypanosome infection. Castellani found the parasite in the cerebrospinal fluid of sleeping-sickness, and his findings have been confirmed by different observers. The disease occurs throughout tropical West Africa, and in recent years has spread through Central and Eastern Africa. Negroes are chiefly affected, but cases have also been observed in Europeans. The infection is transmitted by a biting-fly (*Glossina palpalis*). The parasites develop in the blood, and during this period symptoms may be wanting, or there may be attacks of fever. When the parasites gain access to the cerebrospinal fluid and increase, cerebral symptoms, particularly coma, are produced as the result of meningitis. The disease runs a chronic course and is invariably fatal.

Trypanosomes are also found in the disease known as **Gamba-fever** which occurs in Senegambia and the Congo, both in the natives and Europeans. According to Laveran, it is due to the same species of trypanosomes observed by Castellani in Uganda. Further, trypanosomes are believed to be the cause of **tropical splenomegaly,** which occurs in India, China, Arabia, Egypt, and Tunis, and is characterized by intermittent or remittent attacks of fever associated with marked swelling of the spleen, leading after many months' duration to progressive anæmia and cachexia having a fatal termination. It is probable that the disease known as *Kâla-azâr* (black fever), which is widely distributed through the valley of Assam watered by the Brahmaputra, is related to tropical splenomegaly.

The **life-history of the trypanosomes** is similar to that of the spirochaetes. According to investigations by *Schaudinn* the *Halterida* (*Hæmoproteus noctuæ* of *Celli* and *San Felice*) of the little owl are the sexual stages of a trypanosome which multiplies in the common mosquito, *Culex pipiens,* so that after a complicated wandering through the body of the mosquito, through its bite again reaches the blood of the owl, in which after a period of asexual increase it changes into the familiar male and female Halteridia. The parasite must, therefore, be called the *Trypanosoma noctuæ.* (Whether other members of the genus Halteridium or Hæmoproteus are to be classed with trypanosomes remains to be settled.) Accord-

ing to *Novy* (*Jour. of Infect. Dis.,* 1905) the observations of *Schaudinn* are open to an entirely different interpretation. He believes that the *Trypanosoma noctuæ* and the *Spirochæta ziemanni* of *Schaudinn* probably represent trypanosomes that have multiplied in the mosquito and are not to be considered as stages in the life-history of cytozoa. According to *Novy's* investigations trypanosome infection of birds is widespread. With the trypanosomes there may be associated intracellular parasites, but no constancy can be shown to exist between a given trypanosome and a given cytozoön.

It has not been decided whether **human trypanosomiasis** is due to more than one variety of trypanosome. The different clinical course of the affections makes this probable. In the forms known as *tropical splenomegaly* or *cachectic fever* and *kála-azár,* there are found (*Leishman, Marchand*) in the spleen, liver, bone-marrow, lymph-nodes, and in intestinal ulcers, great numbers of small bodies, partly free and partly intracellular, consisting of an intensely staining ring-shaped chromatin body surrounded by a circular or oval, clear area staining lightly with eosin. Besides the chromatin-body there is often found (*Marchand, Ledingham*) a small, intensely staining round or elongated granule, which is often connected with the chromatin-ring by a delicate stalk. These bodies (*" Leishman-Donovan bodies"*) were first found by *Leishman* and *Donovan* in smears from the spleen, and were later studied by *Marchand, Ledingham, Manson* and *Löw, Bentley, Rogers,* and others, the general opinion being that they represented degeneration forms of trypanosomes. *Rogers* has succeeded in growing them outside the body and in demonstrating their transformation into elongated flagellated organisms resembling trypanosomes. On account of the absence of an undulating membrane *Rogers* believes the organism to be a herpetomonas. *Ross* regards it as a new genus and has called it *Leishmani donovani.* Nothing is absolutely determined concerning the transmission of this fatal infection. *Rogers* believes that it is transmitted by bed-bugs or mosquitoes. *Nicolle* (*Arch. de l'Inst. Pasteur,* Tunis, 1908) has succeeded in cultivating the Leishman-Donovan bodies from cases of *infantile splenomegaly* in Tunis. He regards the protozoön obtained as a new species. *Leishmania infantum.* The protozoa found in a case of tropical sore by *Wright* (*Jour. of Med. Res.,* 1903) and called by him *Helcosoma tropicum,* are regarded as Leishman-Donovan bodies, and designated by *Nicolle* as *Leishmania wrighti.* They are regarded as the infective agent of "Delhi boil."

According to the majority of writers *trypanosome* or *Gambian fever* is but the early stage of *sleeping-sickness,* both conditions being due to infection with the same parasite, the *Trypanosoma gambiense.* The first stage is of variable duration, lasting from three months to three years or longer. During this stage there is polyadenitis and the trypanosomes may be demonstrated in the blood and lymph-nodes. As a diagnostic method the examination of a drop of fluid removed from an enlarged cervical node by means of a hypodermic needle is advised, since the parasites can be found in this way immediately if they are present in the body.

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§ 187. Of the **Sporozoa** occurring as parasites in man and other
mammals, the **coccidia** are to be mentioned first. In their young state
they exist as non-encapsulated inhabitants of epithelial cells, particularly
in those of the intestinal canal and its adnexa, the liver especially, and
more rarely in the organs of excretion. Some of the mature forms sur-
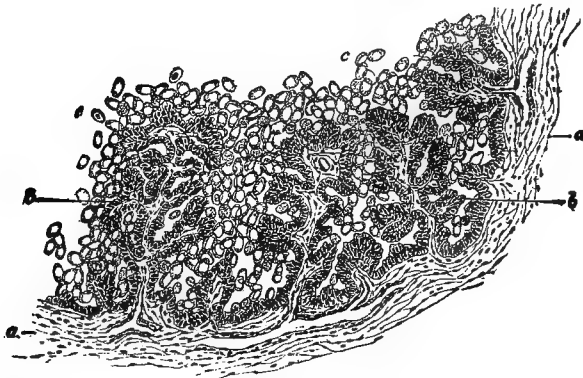
Fig. 483.—Section through the wall of a dilated bile-duct, filled with coccidia and lined
with papillary proliferations. From a rabbit's liver that was studded with coccidia nodules
(Müller's fluid, hæmatoxylin, eosin). *a*, Connective tissue; *b*, branching papillary proliferations
covered with epithelium; *c*, coccidia. × 23.

round themselves with a capsule and become changed into round or oval
permanent cysts or *oöcysts* (Schaudinn), which leave their resting-place
and usually also their host, and under certain conditions form sickle-
shaped *sporozoites* through repeated division of their cell body
(*sporogony*). Through the taking-up of sporozoite-containing oöcysts
into a new host there is produced an infection of the latter, in that the
sporozoites are set free and seek out epithelial cells for their further
development.

Besides this form of multiplication there occurs in the infected organ reproduction by *schizogony* — that is, there are developed from mature but non-encysted individuals, by means of segmentation, a large number of new sickle-shaped individuals, the so-called *merozoites,* which seek out epithelial cells, and develop in them.

Coccidium oviforme (Fig. 484) is a parasite of the intestine and biliary passages, occurring especially in rabbits. Podwyssozki claims to have observed them in the human liver.
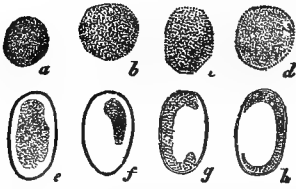
FIG. 484.—Coccidia from the biliary duct of the rabbit's liver (Fig. 483), showing different stages of development (Müller's fluid, hæmatoxylin). *a, b,* Small, coarsely granular young forms; *c, d,* large forms with darkly staining peripheral granules; *e, f, g, h,* oval, encapsulated forms, the protoplasm of which — p a r t l y coarsely granular and partly fine — fills up only a portion of the capsule. × 400.

In the liver of rabbits the invasion of coccidia leads to the formation of white nodules which may reach the size of a hazelnut. These nodules contain a soft, white, or yellowish-white mass, and consist of dilated bile-passages, the inner surface of which is more or less richly furnished with papillary growths (Fig. 483), and whose lumen contains numbers of coccidia.

The coccidia occur in the bile-passages partly in the form of non-encapsulated protoplasmic structures, and partly in the form of encapsulated bodies. The smallest coccidia, which are regarded as the younger forms, exhibit a coarsely granular protoplasmic structure (Fig. 484, *a, b*), within which a nucleus (*a*) may occasionally be demonstrated. The larger forms exhibit on their outer surfaces regularly arranged granules (*c, d*), which stain intensely with hæmatoxylin. The encapsulated forms occur as oval, doubly contoured, clear bodies (*e, f, g, h*) within which lies a variously shaped mass exhibiting various forms of granulation, but never entirely filling the space within the capsule.

To the coccidia belong those **parasites** which **occur in the epidermis**
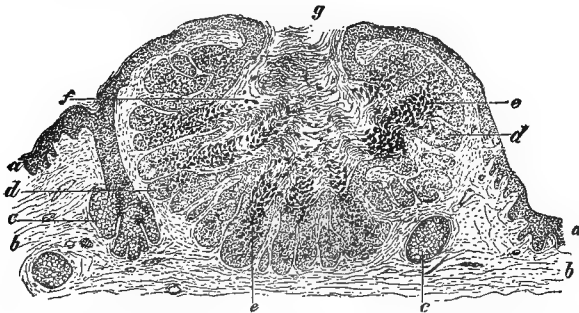
FIG. 485.—Epithelioma contagiosum. Section through greatest diameter (Müller's fluid, hæmatoxylin). *a,* Epidermis; *b,* connective tissue; *c,* sebaceous gland; *d,* gland-like epithelial proliferations; *e,* parasites; *f,* horny cells mingled with parasites; *g,* duct filled with horny epithelium and parasites. × 13.

of man and form peculiar growths known as **epithelioma contagiosum** (Fig. 485). In its fully developed condition the growth consists of a nodule, the size of a pea or larger, which is elevated above the surface of the skin, shows a small groove in its centre, and possesses a waxy lustre.

On section there may be seen a lobulated epithelial growth (Fig. 485, *d*),

with a central cavity opening externally (g), thus resembling a gland; it has many times been mistaken for a hypertrophic sebaceous gland. It represents an independent new-formation of epithelium due to a parasite. The parasites develop inside the epithelial cells of the growth (e), but are pressed by the growth of adjacent epithelium toward the central cavity (f), and lie in a meshwork of desquamated and horny epithelial cells.

The earliest stages of development of the parasites occur in the epithelial cells as small protoplasmic bodies (Fig. 486, a, b), which can be distinguished from the cell-protoplasm only with difficulty; occasionally they contain in their interior small, distinct granules, and are therefore more evident. Later they increase in size, and finally fill the cell (c, d, e), pressing the nucleus to one side. At the same time the granules in the cell (c) increase, and grow to larger bodies, so that the parasite finally becomes divided into a greater or less number of well-defined structures (d, e, f) lying in a finely granular network. The nucleus of the epithelial cell is destroyed during this time.

FIG. 486.—Parasites of Epithelioma contagiosum in various stages of development, lying inside epithelial cells (Müller's fluid, hæmatoxylin). a, b, Epithelial cells, enclosing a protoplasmic body inside of which lie single large granules; c, epithelial cell almost completely filled with parasites; d, e, f, parasites completely filling the epithelial cells, and divided into numerous separate bodies lying in a granular network; the cell-nucleus has been destroyed in f. × about 500.

FIG. 487.—Miescher's sacs, from swine-muscle. a, b, Muscle cut longitudinally and transversely. × 100. c, Longitudinal section. × 580.

The epithelial cells which enclose parasites develop early a distinct membrane, which becomes more and more clearly defined, and surrounds the parasite. The parasites which are expelled from the cells form oval bodies enclosed in a capsule and present a homogeneous appearance. They stain deeply with hæmatoxylin.

The contagious epitheliomata may appear in great numbers in one and

the same individual, and several persons living together may be simultaneously or successively attacked.

By many writers the molluscum bodies are not believed to be parasites, but are regarded as hyaline or horny products of cell-degeneration.

Our knowledge of the significance of the so-called **Miescher's sacs** is still incomplete. They are tube-shaped structures which are not infrequently found in the muscles of the hog (Fig. 487, *a, b*), cattle, sheep (especially in the œsophagus), and mice. They vary in size, and lie in the muscle-fibres. In mature parasites the contents of the tubes are differentiated into single segments defined by a membrane (Fig. 487), which enclose spherical (*c*), kidney-shaped, or sickle-shaped bodies. The
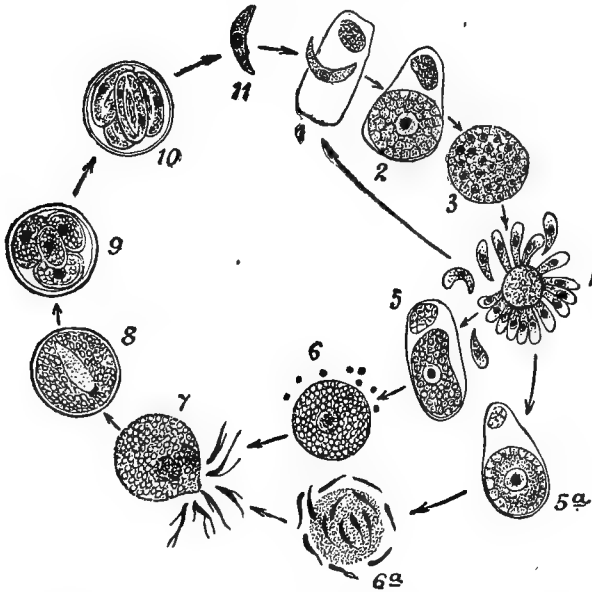
FIG. 488.—Cycle of development of *Coccidium Schubergi*. (After Schaudinn and Lühe). 1, Sporozoite (or merozoite) penetrating into an epithelial cell; 2, mononuclear schizont in an epithelial cell; 3, multinuclear schizont; 4, division of the schizont (schizogony) into numerous merozoites; 5, macrogamete (female cell) arising from a merozoite; 6, fully developed marcogamete surrounded by extruded chromatin granules; 5*a*, microgametocyte (male cell) arising from a merozoite; 6*a*, microgametocyte surrounded by loosened microgametes (spermatozoa); 7, fertilization of the macrogametes by microgametes; 8, young oöcysts; 9, oöcysts with sporoblasts; 10, oöcysts with sporocysts, each containing two sporozoites; 11, sporozoite.

parasite is classed with the **Sarcosporidia**. The separate segments are designated *sporocysts* or *sporoblasts,* since within these the round or sickle-shaped *spores (Rainey's bodies)* arise. From the latter, new Miescher's sacs may develop under favorable conditions (Pfeiffer). Ingestion of meat containing sarcosporidia is not dangerous to man, although sarcocysts have been observed in man in the muscles, heart, intestine, and liver.

As early as 1870 *Eimer* published observations on the development of coccidia, but their life-history has been accurately determined only in recent years through the investigations of *R. Pfeiffer, Simond, Lèger, Schaudinn, Schuberg, Siedlecki, Schneider, von Wasielewski, Labbé,* and others.

The **reproduction of coccidia** occurs (*Lühe*) partly through *sporogony,* partly through schizogony. The first method serves for the spreading of infection and the preservation of the species, the second increases the extent of the infection in the infected host. *Sporogony is closely connected with a previously occurring copulation* which in its course suggests the fertilization of the egg of the metazoa. *Alternation of generations* also takes place.

· The development and reproduction take place in the following manner : In schizogony the sickle-shaped germ (Fig. 488, 1) arising as a *sporozoite* or *merozoite* develops within an epithelial cell into a schizont (2) in which there soon takes place multiplication of the nucleus (3). There then results (on the second day after the over-feeding of sporocysts) formation of merozoites (4) corresponding in number to the nuclei, and a residual body which is left behind after the segmentation.

The merozoites again seek epithelial cells, and the same development begins anew. If the affected organ, as the result of these processes, becomes overcrowded with parasites, there are then formed sexual individuals (*Schaudinn*). Some of the merozoites grow into large cells, the *macrogametes* (5, 6) or female cells, which, when mature throw off a portion of their chromatin-substance (6), and either remain naked or surround themselves with a capsule, which is provided with a micropyle. At the same time other merozoites develop into the male sexual cells or *microgametocytes* (5a, 6a), the nuclei of which divide into many daughter-nuclei. The latter approach the surface of the cell, and, surrounded by a certain amount of protoplasm, are constricted off, (6a) and then represent the *microgametes* (corresponding to the spermatozoa of the higher animals). The *copulation* of the microgametes with the macrogametes takes place in a manner similar to that of the fertilization of the metazoan egg, in that the microgamete penetrates the encapsulated form of macrogamete through the micropyle and the naked form through a certain point which pushes itself outward to form a prominence (7), the conceptional protuberance. *Sporogony* follows the fertilization — that is, the oöcyst (8) is formed, in which, through division of the nucleus and protoplasm, there arise four *sporoblasts* (9), each of which later produces two sickle-shaped *sporozoites* (10).

Numerous authors hold the view that local pathological conditions of the tissues in man other than those described above may be referred to *sporozoa,* particularly *carcinoma, Darier's disease, Paget's disease,* peculiar diseases of the urinary passages, etc. It may, however, be remarked that this assumption in part is based on error, and has not been proved by investigations made up to the present time.

So far as *carcinoma* is concerned, in spite of the great number of works on the subject, so numerous indeed that they can scarcely be perused (cf. § 121), no proof has been given that protozoa, coccidia in particular, are present in the epithelial proliferation and are to be regarded as the cause of the same. All the appearances described as occurring as carcinoma cells, even the sickle-shaped formations which have been thought to be convincing and those provided with a sort of capsule, may be otherwise interpreted, and may be explained as changed nuclei, as altered protoplasm of the cancer-cells, as cell excretions, and finally as a product of cell-fusion or of the taking up of leucocytes by the cancer cells.

The disease described by *Darier* as *psorospermose folliculaire végétante,* and referred by him to the presence of sporozoa, is probably an inflammatory affection of the skin characterized by pathological cornification (keratosis follicularis of *von Withe*), in which horny plugs and pegs are developed successively in the epithelium of certain parts of the body, while the cutis shows slight inflammatory changes. According to *Buzzi, Miethke, Rieck, Krösing, Petersen,* and others, the *" corps ronds,"* described by *Darier* as parasites, contain kerotohyalin and eleidin, substances which are present in cornified cells but not in gregarinæ.

Paget's disease is an affection spreading from the nipple, beginning with an eczema-like inflammation, and leading to superficial ulceration, and ending in carcinomatous infiltration of the skin. It has been referred by *Darier, Wieckham, Malassez,* and others to the presence of a parasitic sporozoon in the epithelial cells; but is, however, either eczema arising from other causes, and leading to cancer, or a primary cancer accompanied by inflammatory processes (*Ehrhardt*), in which peculiar changes take place in the epidermis, particularly swelling of the protoplasm and nuclei, with formation of vacuoles, and proliferative changes, the peculiar appearances of which might be mistaken for parasites. According to *Jacobaeus* these appearances are brought about through penetration of the carcinoma into the superficial epithelium.

In **variola** and **vaccinia** there occur constantly in the epithelium that has undergone recent changes small lightly staining bodies surrounded by a clear zone, often in great numbers. Their constant occurrence in repeated inoculations and their characteristics make it very probable that they represent parasites belonging to the protozoa, and this view is favored by numerous authors (*Guarnieri, E. Pfeiffer, L. Pfeiffer, Bosc, Funk, Councilman, von Wasielewski,* and others). *Hückel* and *Borrel* have attempted to interpret these structures in another way.

Negri ("Etiologie der Tollwut," *Z. f. Hyg.,* 43 und 44 Bd., 1903) describes **small bodies** found in the nervous system of dogs inoculated subdurally with the **virus** of **rabies** that he regards as protozoa and considers to be the cause of rabies. Investigations by *Volpino* ("Struttura dei corpi descr. da Negri nella Rabbia." *A. per le Sc. Med.,* xxviii., 1904), and by *Luzzani* ("La dimonstraz. del Parass. specif. in un caso di rabbia nel l'uomo." *Ibid.*) support the view of *Negri,* but offer no further information as to the nature of the parasite. According to *A. W. Williams,* the Negri bodies possess a definite chromidium and are, therefore, to be classed with the rhizopods (*Journ. of Infect. Dis.,* 1906).

Mallory ("Scarlet Fever." *Jour. of Med. Res.,* x., 1904) found a protozoön-like body in four cases of **scarlet fever.** *Field* (*Journ. of Exper. Med.,* 1905) believes that these bodies are products of degenerating tissue-cells and leucocytes. *Gotschlich* ("Protozoenbefunde im Blute von Flecktyphuskranken." *D. med. Wochenschr.,* 1903) found pear-shaped bodies in six cases of **typhus fever** that resembled the parasites of Texas fever, and in four cases he also found flagellated bodies.

According to *Hess* and *Guillebeau,* coccidia may occasion in young cattle diseases of the intestine resembling dysentery. According to *Olt* and *Voisin,* the shotty eruption of swine characterized by the formation of little cysts in the skin is caused by coccidia (*C. fuscum*), but according to *Lühe* the description of the parasites does not correspond to coccidia.

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(*Coccidia; Parasite of Epithelioma Contagiosum; Miescher's Sacs.*)

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§ 188. Under the designation **Plasmodium malariæ** (Marchiafava and Celli) or the **hæmosporidia** of **malaria** are grouped those parasites which are regarded as the cause of human malaria. The parasites are found in the blood of malarial patients in different forms, usually enclosed in cells; and, according to the observations of Golgi, Celli, Marchiafava, and others, a definite relation can be demonstrated between the number and the stage of the development of the parasite and the attacks of fever. The parasites pass through different stages of development in the interval between the attacks of fever, these stages, according to the authors mentioned, differing in *febris quartana, febris tertiana,* and *febris quotidiana.* At the same time the parasites of the different forms of fever exhibit certain differences in their physiological characteristics.

Supported by these facts, there may therefore be distinguished in man different species of the malarial plasmodium. In its narrower sense the designation *Plasmodium malariæ* is used only with reference to the parasites of quartan fever. The parasite of vernal tertian on account of its active movements is known as *Plasmodium vivax* (Grassi and Feletti); and the parasite of tropical malaria, which in Italy appears in the autumn, is designated *Plasmodium præcox*.

Schaudinn's classification of the malarial parasites is accepted by most writers. He recognizes three varieties: *Plasmodium vivax* (tertian), *Plasmodium malariæ* (quartan), and *Plasmodium immaculatum* (æstivo-autumnal parasite).

The development and increase of the plasmodia take place within the red blood-corpuscles, in which, first of all, small, colorless amœboid
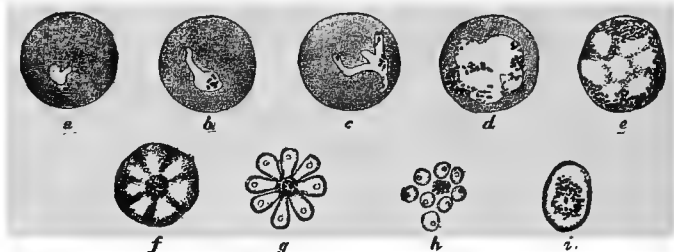
FIG. 489.—*Plasmodium malariae* of quartan fever, in different stages of development. (After Golgi.) *a*, Red blood-cell with a small non-pigmented plasmodium; *b*, *c*, *d*, *e*, pigmented plasmodia of varying size inside the red blood-cells; *f*, plasmodium in beginning segmentation, with centrally placed pigment; *g*, segmented plasmodium; *h*, plasmodium divided into separate spherules; *i*, free gamete (sexual individual).

bodies (Fig. 489, *a*) appear. In *quartan* fever the further development of the parasite proceeds by enlargement of the small amœboid forms (Fig. 489, *a*, *b*, *c*, *d*, *e*), so that the red cell becomes more and more filled by the parasite. At the same time pigment-granules appear within the bodies of the plasmodia. When the plasmodia have attained a certain size, the pigment-granules move toward the centre, while at the same time a radiating cleavage sets in, and daisy-like figures ("*rosettes*") (*f*, *g*) are formed, which consist of a pigmented centre and non-pigmented, radiating club-shaped petals. Later the clubs become detached from the central mass of pigment and take on a circular form (*h*).

According to Golgi, the development and division of the plasmodia of quartan fever require three days for completion, and the attacks of fever coincide with the division of the plasmodia. The red cells occupied by the parasites are destroyed; the young plasmodia formed by division penetrate into blood-corpuscles, and the cycle of development begins anew. The pigment-granules formed by the plasmodia are taken out of the circulating blood partly free and partly enclosed in cells, and are deposited in different organs, particularly in the spleen, liver, and bonemarrow.

In *febris tertiana* (*vernal tertian*) the cycle of development is completed in two days. The plasmodia developing within the red cells (Fig. 490, *a-d*), which are designated *Plasmodium vivax,* show much livelier motion and lead much more quickly to decolorization of the red bloodcorpuscles than those of quartan fever; the red cells become decolorized on the first day after the fever, while the plasmodia are still small. The

protoplasm of the plasmodia of tertian fever is also more delicate and less sharply contoured and the pigment-granules are smaller. In its division each plasmodium splits up into from fifteen to twenty new cells

FIG. 490.—*Plasmodium vivax* of a vernal tertian, showing different stages of development. (After Golgi.) *a*, First stages of development; *b, c*, enlarged plasmodia with pseudopodia; *d*, plasmodia before sporulation, the red blood-cell decolorized; *e*, sporulation; *f*, free parasite with flagellum (micro-gametocyte).

(*e*), while the parasite of quartan fever forms only from six to twelve. According to Celli and Marchiafava, sporulation not infrequently occurs prematurely, from five to ten spores arising within a red corpuscle.

The parasite of tropical or *pernicious malaria,* the *plasmodium præcox,* differs from the hæmosporidia of the vernal fevers, particularly in the fact that it is smaller (Fig. 491, *a, b, c, d*) and executes lively movements within the red cells. It completes its life-cycle in twenty-four to forty-eight hours.

Through the formation of a central vacuole it often appears in the form of a ring. During the stage of multiplication the parasite collects in the internal organs, so that division-figures (*d*) must be sought in the spleen, liver, bone-marrow, and brain (where they are present in great numbers). Some of the infected red cells become crenated and prickly, and of a brassy color (Marchiafava, Celli); they die prematurely, and blood-cells which contain no parasites are also destroyed. The attacks of fever can in the case of autumnal tertian fever become so prolonged that they pass into one another, and the condition thereby assumes the character of a *sub-continuous* or *continuous fever.*

According to Marchiafava and Celli, there also occurs a quotidian parasite similar to the latter, but producing no pigment at all.

Nuclear bodies may be demonstrated, during certain stages of development, in the

FIG. 491.—*Plasmodium præcox* of tropical malaria, showing different stages of development. (After Golgi and Sanfelice.) *a*, First stages of development; *b*, plasmodia with pseudopodia; *c*, round plasmodium with pigment, before segmentation; *d*, sporulation; *e*, intraglobular sexual individual; *f, g*, free sexual cells.

protoplasm of all the endoglobular forms of malarial hæmatozoa. According to Ziemann, in *sporulation* there first occurs *division of the chromatin into small clumps,* and later division of the cell-body, so that every clump of chromatin is surrounded by a zone of protoplasm.

Besides the forms of development which lead to intracellular increase of the plasmodia through *schizogony,* there occur extraglobular, also endoglobular, round and oval, sickle- or crescent-shaped structures (Figs. 489, *i;* 491, *e, f*), as well as round bodies with flagella (Figs. 490, *f;* 491, *g*) which also contain a nucleus and pigment. The crescent forms occur

particularly in the pernicious fever (Fig. 491, *e, f*). Celli regards them as diagnostic of this form of fever; Ziemann also holds that typical crescents are not formed in other varieties of malaria.

The last-named forms Laveran described as structures belonging to
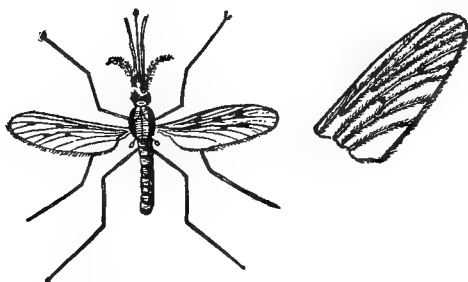
FIG. 492.

FIG. 493.

FIG. 492.—*Anopheles claviger.* (After Meigen, *loc. cit.*) × 4. To the right a wing at higher magnification.
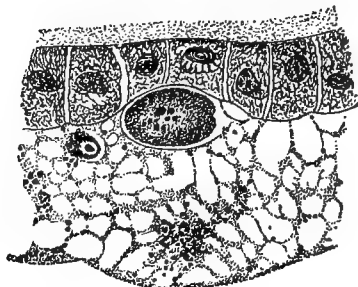
FIG. 493.—Oökinete of human pernicious malaria (*Plasmodium praecox*) in the intestinal wall of a mosquito. (After Grassi.)

the cycle of development of the plasmodia, while Golgi, Canalis, Celli, Marchiafava, Bignami, Bastianelli,, Ziemann, and others regarded them as sterile vegetation-forms that die without further development. First through the investigations of Manson, Bignami, Ross, and MacCallum, to which were later added those of Grassi, Bastianelli, Bignami, Celli, Laveran, Koch, Schaudinn, and others, it was shown that the *crescents,*
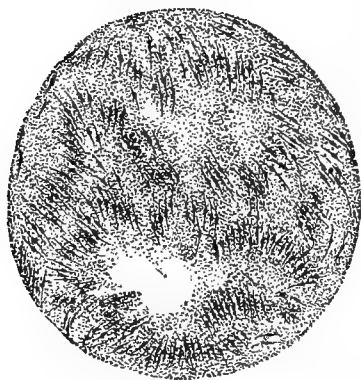
FIG. 494.—Oöcyst of *Plasmodium prae-cox*, filled with sporozoites. (After Grassi.)

the *oval bodies,* the *spherical bodies,* as well as the *flagellated bodies* known as *polymitus, are intended for repro-duction by copulation.* The flagella-producing hyaline spheres arising from the crescents are *male sexual individ-uals* or *microgametocytes,* and the flagella developing from them, in whose formation the chromatin of the cell takes an essential part (Sach-aroff), have the significance of *seminal cells, spermatozoa,* or *microgametes;* while the non-flagellated spheres arising from the granular crescents have the significance of *female sexual cells* or *macrogametes.* The crescents leading to the formation of the sexual cells ap-pear only after infection has lasted for several days. In the chronic cachexia following malaria the forms lead-ing to schizogony are absent, and the crescents alone are present.

The *copulation of the malarial parasites* of man takes place normally in the *stomach of the mosquito,* in different *species of Anopheles* (Fig. 492), which take up parasites during the sucking of blood from malarial patients.

The *copula* arising from the union of the macrogamete and microgamete is designated *oökinete* (Schaudinn), a long, motile structure which penetrates into the stomach-wall of the mosquito (Fig. 493), where through the formation of a capsule it becomes the *oöcyst.* The latter then enlarges, and forms numerous daughter-nuclei, and then *sporoblasts,* which break up into the *sporozoites* (Fig. 494) and the residual body. According to Grassi, as many as 10,000 sporozoites may be formed in one oöcyst.

The sporozoites, which are formed in enormous numbers, pass into the body-cavity after the rupture of the oöcyst, and collect principally in the salivary glands, and through the bite of the infected mosquito are again transmitted to man, in whose blood they multiply within the red blood-cells through schizogony.

The *pathogenic significance of the malarial plasmodia* rests on the destruction of red blood-cells. In the pernicious form this may be so extensive that hæmoglobinuria may take place. The melanotic pigment formed in the parasite is a product of the vital activity of the parasites. In addition, as the result of the destruction of hæmoglobin, there occur deposits of hæmosiderin in the bone-marrow, spleen, liver, and occasionally in the kidneys. In marked destruction of the red blood-cells there may occur excretion of dark red urine, hæmoglobinuria (*blackwater fever.*) The massing of the parasites of pernicious malaria in the cerebral capillaries may cause circulatory disturbances with the occurrence of numerous hæmorrhages, and severe cerebral symptoms.

As the result of retention of pigment-containing malarial parasites and the deposit of the products of blood-destruction, there occurs marked swelling of the spleen associated with hyperæmia, followed by tissue-degenerations and by tissue-proliferations.

After a long duration of the process the spleen may become markedly enlarged, pigmented, and greatly changed in structure. Likewise, in the liver there may be found degenerations and pigmentations, and also indurative proliferations.

Certain varieties of the plasmodium correspond to the individual types of fever, as given above, but it must be noted that the fever-forms known as quotidian, subcontinuous, and continuous (*"comitata"*) may also arise through the presence in the blood of different generations of the plasmodia of tertian or quartan fevers, so that daily a portion of the parasites comes to sporulation. In this way there arise quotidian forms of fever, which must be regarded as a double tertian infection or as a triple quartan.

According to Schaudinn, the *relapses* that occur sometimes weeks and months after the original attack may be explained by the fact that the macrogametes, which are longer-lived, revert to schizonts by throwing off a portion of their nucleus and protoplasm. According to Plehn, basophile granules are found in the red blood-cells as long as the infection persists. They vanish when the infection comes to an end.

The malaria occuring in northern countries corresponds in general to the vernal forms of Italy, while the æstivo-autumnal form is found in the tropics.

Hæmosporidia — that is, sporozoa which live at the cost of the red blood-cells, and thereby produce diseases which are to be classed with malaria — occur frequently in animals. Those of **birds** are best known (*Danilewsky, MacCallum, Ross, Grassi, Dionisi, Celli,* and *Schaudinn*) and the life-cycles of the hæmosporidia of the pigeon, owl, and skylark have been determined. *Labbé* distinguishes two

genera in birds, *Halteridium* and *Proteosoma* (*Hœmoproteus* of *Kruse*) ; as to the number of undifferentiated species, nothing can be said at the present time. *Celli* obtained from the birds mentioned three well-defined species. *Schaudinn* assigns the parasites of birds designated as proteosoma to the genus plasmodium.

Of the **Mammalia,** cattle in particular suffer in different countries (Southern States of North America, Italy, South Africa, Roumania) from malaria characterized by high fever and hæmoglobinuria. In the malaria of cattle known as *Texas-fever, Smith* and *Kilbourne* found in the red-blood cells a small, often pear-shaped, and paired parasite (*Piroplasma bigeminum*), whose pathogenic significance they determined through the inoculation of healthy cattle with blood containing the parasites. *Babes* found the same parasite in the epidemic **hæmoglobinuria of cattle** prevalent in Roumania. The first-named observers showed that infection takes place through parasitic ticks (*Boöphilus bovis*) living on the cattle, the infection being transmitted, not by the same tick which takes up the infected blood, but through the generation descending from the same. This mode of infection was confirmed by *Koch* in the hæmoglobinuria of cattle occurring in German East Africa and by *Grassi* in that occurring in cattle in Italy. The mode of development of the *piroplasma* in the body of the tick is still unknown; and it therefore cannot be decided whether the parasite should be classed with the known malaria parasites. Against a near relationship with the latter is the fact (*Lühe*) that it increases in the red blood-cells by repeated simple division. According to *Kolle,* there occurs in South Africa, besides Texas-fever, another malarial disease of cattle (*Febris malariaformis*), which is caused by an endoglobular parasite. *Theiler* also distinguishes two forms of piroplasmosis of cattle in South Africa. The piroplasma occurring in dogs and in horses he regards as a form distinct from Piroplasma bigeminum. According to observations by *Nocard* and *Almy* and *Motas* piroplasmosis associated with hæmoglobinuria is not uncommon in dogs in France. According to *Galli, Valerio,* and *Piana,* it also occurs in Italy.

According to *Bonome* and *Celli,* hæmosporidia also cause malaria in *sheep* and *lambs,* according to *Koch* and *Kassel* in apes, and according to *Dionisi* in bats; but the life-history of these parasites is unknown.

Danilewsky and *Celli* have described hæmosporidia in the *frog,* and the latter observer determined the development of the parasite in the blood.

Whether the malarial parasites of man can be transmitted to animals, or whether the malaria of animals can lead to infection of man through the medium of mosquitoes, is not decided with certainty, but it appears improbable. The plasmodia of the bat most closely resemble those of man, yet attempts at inoculation made by *Dionisi* gave no positive results. It may therefore be assumed that malaria would die out in a given region, either when all susceptible anopheles were killed, or all infected human individuals healed or protected from mosquito bites.

The malarial plasmodia are stained best by the Romanowski stain, which differentiates the nulceus.

The view that **mosquitoes** were concerned in the distribution of malaria is old, and has obtained in Italy since Roman times. *Koch* found it a popular belief among negroes. *Manson* (1896) and *Bignami* (1896) were the first to turn their attention to the problem and to give hypotheses concerning the rôle played by mosquitoes in the spread of malaria. *Bignami* carried out experiments along this line, but came to no positive result. *Ross* was the first (1897-98) to determine the cycle of development of the malarial plasmodium of birds (usually known as proteosoma). According to his investigations, the parasites taken up with the blood of the infected bird into the intestinal canal of mosquitoes penetrate into the intestinal wall, and there change into cysts in which innumerable rod-shaped germs develop. Becoming free, these germs gain entrance into the salivary glands of the mosquitoes, and thence into the organism of the bird during the act of blood-sucking. Ross found the parasites in the blood of the infected bird in from five to nine days after infection.

About the same time, *Grassi* found that the distribution of malaria in man corresponded to the distribution of *Anopheles claviger* (*Fabricius*) (Fig. 492), and not to that of the common mosquito (*Culex pipiens*). Basing his experiments on this observation, *Bignami* succeeded in producing malaria in healthy men by means of the bite of anopheles. Later *Grassi* in coöperation with *Bastianelli* and *Bignami,* succeeded in determining the life cycle of the malarial parasite. It was then shown that several species of anopheles native in Italy (*Anopheles claviger* [*Fabricius*] or *Anopheles maculipennis* [*Meigen*], *Anopheles superpictus, pseudopictus, bifurcatus*) spread the malaria occurring in man, while *Culex pipiens* is the host of the parasites of bird-malaria.

The **cycle of development of the malarial plasmodium** is as follows: Within the blood (of man as well as of birds) multiplication takes place first by *schizogony*. The young form of the plasmodia, represented by a small, unpigmented body, grows in the red cells (Fig. 495, 1) into a larger body (2), in whose central portion pigment-granules collect. This cell-body known as *schizont* shows in preparation for schizogony an increase of nuclei (3), and then divides into a number (varying with the species) of *spores* or *merozoites* (4) with the abandonment of a pigmented residual body. The merozoites then seek a red blood-cell (1), and the cycle is again begun.

In *sporogony* the merozoites develop into sexual individuals, macrogametes (5) and microgametocytes (5a). When taken up into the stomach by blood-sucking mosquitoes, the sexual individuals become ripe for fertilization, the macrogamete by throwing off the karyosome (6), the microgametocyte through the formation of microgametes (6a). Copulation then follows (7). From the copula arises the motile oökinete (8), which in the wall of the mosquito's intestine becomes the oöcyst, in which through the division of the nucleus the sporoblasts (9) are formed, which in turn break up into a large number of sporozoites (10), which (11), becoming free, collect chiefly in the salivary glands, and are thence transferred by the bite of the mosquito to a new host, in whose blood they increase through schizogony (1–4).

According to the investigations of *Schaudinn,* the macrogametes and the microgametocytes of *Plasmodium vivax* may be distinguished from each other in the earliest stages of development in the red blood-cell, and also from the schizonts, at first through the peculiar structure of the nucleus and later through that of the protoplasm. In a new infection of tertian malaria the differentiation of the gametes began after the third attack. The growth takes place essentially slower than in the case of the schizonts. The pigment production is more abundant, while the nucleus is larger and less dense.

FIG. 495.—Cycle of development of *Proteosoma.* (After Schaudinn and Lühe.) 1, Sporozoite (or merozoite) within a red blood-corpuscle; 2, schizont; 3, schizont with numerous nuclei; 4, schizogony, formation of merozoites; 5, macrogamete (female cell) arising from a merozoite; 6, fully developed macrogamete after extrusion of the karyosome; 5a, microgametocyte (male cell) arising from a merozoite; 6a, microgametocyte surrounded by loosened microgametes (spermatoza); 7, fertilization of the macrogamete; 8, oökinete; 9, oöcysts with sporoblasts; 10, oöcysts with sporozoites; 11, free sporozoite.

The larvæ of anopheles live chiefly in slowly flowing water. The eggs of *Anopheles claviger* require about thirty days at 20°–25° C. for the development of the insects, and these in turn lay eggs when twenty days old. The pupæ are resistant to drying, to cold, and to contamination of the water. The mosquitoes fly during the evening and night, but do not rise very high above the level of the earth, and do not go very far away from the place of development. According to *Grassi, Bignami,* and *Bastianelli,* the æstivo-autumnal parasites will not develop in anopheles at a temperature of 14°–15° C., and grow only slowly at 20°–29° C.; at 30° C. they complete their entire development up to the formation of sporozoites in about seven days.

The literature concerning malarial parasites is extremely rich. The results of the latest investigations are given in the publications of *Grassi, Schaudinn, Mannaberg, Nuttall, Celli, Marchiafava, Bignami,* and *Lühe.*

35

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§ 189. Of the **ciliates** or **infusoria** occurring within the human organism the best known and most important is the **Balantidium** or **Paramæcium coli,** a unicellular animal 60-70 μ long, covered with short uniform cilia. At its anterior end it has a short peristoma (Fig. 496, *a*) which opens into a short gullet. The body is marked with parallel stripes and encloses a bean-shaped chief nucleus (*b*) and an accessory nucleus and two vacuoles. Multiplication takes place by division into two new individuals. It develops a permanent form in the shape of a spherical cyst with a firm membrane.

Balantidium coli occurs often in the colon of swine without causing apparent changes. In cases of chronic diarrhœa in man it has been found in the dejections and in the colon, and probably stands in causal relation to the intestinal catarrh. According to investigations by Solowjew, Askanazy, Klimenko, and others the balantidia may penetrate into the mucosa and submucosa of the intestine and cause ulcers. They may also wander into the blood-vessels.

FIG. 496.—*Balantidium (paramaecium) coli,* with two contractile vacuoles. (After Claus.) *a,* Mouth; *b,* nucleus; *c,* included starch grains; *d,* foreign body in the act of being extruded. High magnification.

·Other species of **ciliates** have been observed in the intestine of man, *Balanti-dium minutum* (*Schaudinn,* 1899) and *Nyktotherus faba* (*Schaudinn*). In the paunch and reticulum of ruminants, in which cellulose digestion is carried on, and in the blind intestine of horses, infusoria are universally present and occur in enormous numbers, for example *Isotricha prostoma, Entodinium caudatum, Ophryoscolex caudatus,* and others.

II. Vermes (Worms).

A. PLATYHELMINTHES (FLAT-WORMS.)

1. *Trematoda, Sucking Worms.*

§ 190. The **Trematodes** or sucking-worms, are flat-worms of tongue or leaf shape. They possess a clinging apparatus in the form of ventral sucking-cups of varying number, and are sometimes furnished with hooks or clasp-like horny projections. The intestinal canal is without an anus, and is usually forked. The development takes place either by the direct growth to maturity of the embryos (*miracidium*) hatching from the eggs, or by alternate generation through the *formation of germs within the host.* The miracidium, or ciliated embryo, penetrates into a snail or mussel, and there grows into a *germ-sac* (*sporocyst*), within which there develops, either directly or after the formation of an intermediate generation of germ-sacs (*rediæ*), a swarming generation of *cercariæ,* which are provided with rudder-like tails. These lose their tails and penetrate into a new host (mollusks, arthropods, fish, amphibia), become encapsulated, and attain sexual maturity as soon as they reach the final host. The germ-sacs which produce cercariæ are designated primary germ-sacs; if they first form rediæ and then cercariæ, they are called secondary germ-sacs.
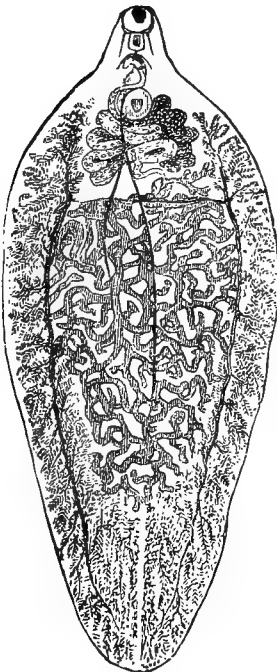
FIG. 497.
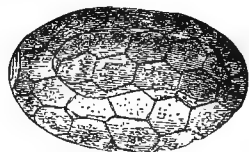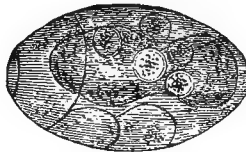
FIG. 498.

FIG. 497.—*Distoma hepaticum* with male and female sexual apparatus. (After Leuckart.) × 3.2.

FIG. 498.—Eggs of Distoma hepaticum. (After Leuckart.) × 200.

Distoma hepaticum, or liver-fluke, is a leaf-shaped sucking-worm about 28 mm. long and 12 mm. broad (Fig. 497). The cephalic end projects like a beak, and bears a small sucking-cup, in which the mouth is placed. Close behind this, on the ventral surface, is a second sucking-cup, and between the two lies the sexual orifice.

The uterus consists of a convoluted, globular sac behind the posterior sucking-cup. On each side of the hinder part of the body lie the yolk-sacs, and between are found the testicular canals, which branch many times. The forked intestinal tract (not visible in Fig. 497) is repeatedly branched.

The eggs (Fig. 498) are oval, 0.13 mm. long and 0.08 mm. broad. In water there develops an embryo, the *miracidium* (Fig. 499, *A*), with cellular germ-balls (*a*); with the aid of its ciliated covering the embryo swims about, and seeks out a new host from the family of the mollusks (*Limnæus minutus*). On penetration into the snail the cutaneous layer is thrown off, and the *miracidium,* which possesses an intestine, an excretion-organ and a brain-ganglion, becomes changed into a *sporocyst* (*B*), in which the intestine and nervous system atrophy, while the cellular germ-balls (*B, a*) form a *second generation of germ-sacs,* the *rediæ* (*B, b*). The rediæ (*C*), which possess an intestine (*C, a*), produce then
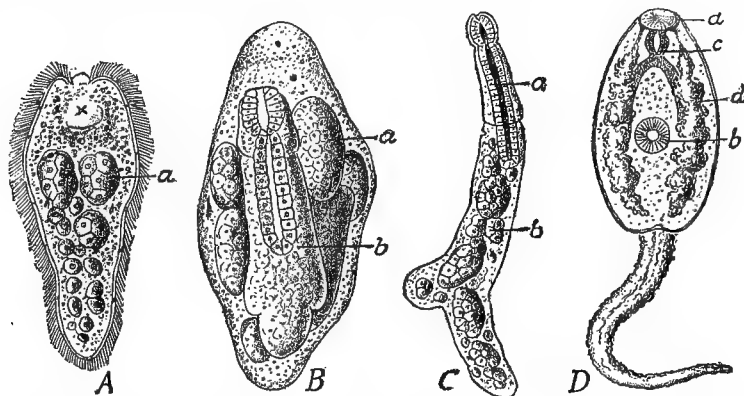
FIG. 499.—Development of the liver-fluke. (After Leuckart.) *A,* Miracidium with germ-balls (*a*); *B,* sporocyst with germ-balls (*a*) and rediæ (*b*); *C,* redia, with intestine (*a*) and germ-balls (*b*); *D,* cercaria with mouth (*a*), abdominal sucking-cup (*b*), intestine (*c*), and glands (*d*).

within the same host the *cercariæ* (*D*) from cells which are loosened from their germ-matrix (*C, b*); these abandon the host and with the aid of a rudder-like tail swim about in the water. With the loss of their tails they become encysted on almost any foreign body, and reach their final host (usually through the food), in which they attain sexual maturity. The sexually mature animal inhabits the biliary passages; more rarely it is found in the intestine or inferior vena cava. The liver-fluke is rare in man but common in cattle and sheep. The results of its invasion, especially when it is present in great numbers, are obstruction and ulcerative strictures of the bile-passages, formation of biliary concretions, inflammation of the tissues in the neighborhood of the bile-ducts, and hyperplasia of the periportal connective tissue with atrophy of the glandular tissue. The same changes are found in cattle. In sheep, following marked invasion of the liver, there may develop a general cachexia.

Distoma lanceolatum is only 8-9 mm. long and 2-2.5 mm. broad, is lancet-shaped, and the cephalic portion is not especially marked off from the body (Fig. 500).

The skin of the body is smooth. Two irregularly lobed testicles (*h*) lie close behind the ventral sucking-cup, in front of the ovary (*o*) and

the uterus (u), the coils of which shine through the transparent body. The anterior coils are black with the ripe eggs, the others are rusty red. The yellowish-white yolk-sacs (d) lie in the middle of the lateral margin.

The oval eggs are 0.04 mm. long, and while still in the uterus contain an embryo which escapes only after several weeks following the casting-off of the eggs. Its metamorphoses are unknown.

Distoma lanceolatum likewise inhabits the bile-passages, but is rare in man. It is of frequent occurrence in sheep and cattle. When present in small numbers, it causes no marked changes; but large numbers may excite inflammation and proliferation of the periportal connective tissue.

Distoma spathulatum (Fig. 501) is a sucking-worm occurring in man in Japan and China. It is 10-14 mm. long and 2.5-4 mm. broad. The eggs are 0.027-0.03 mm. long and 0.015-0.018 mm. broad. The parasite inhabits usually the bile passages and gall-bladder, but may gain access to the pancreatic duct (Katsurada), and pass into the intestine. When occurring in great numbers (Katsurada counted 4,361 in one case) it causes obstruction to the outflow of the bile, and often excites more or less severe inflammation and proliferation of connective tissue.

The parasite is found also in cats and dogs (Katsurada).

Distoma Westermanni (Kerbert), or Distoma pulmonale (Baelz) occurs in Japan, China, and Corea. The worm is 7.5-10 mm. long, 5-7.5 mm. broad, egg-shaped, with slightly flattened ventral surface. The oval eggs are 0.09 mm. long and 0.056 mm. broad. The internal organization (Fig. 502) resembles that of the other trematodes. It occurs in man as well as in cats and dogs (Katsurada). It is found most frequently in the lungs, but occurs in other organs: the pleura, brain, liver, intestinal wall, peritoneum, orbital cavity, eyelid, scrotum, etc. In each case it occupies small cavities surrounded by newly formed connective tissue, and occurs occasionally in pairs. In the lung it may be found in the bronchi, the walls of which show inflammatory changes (Katsurada). Its presence in the lung may give rise to hæmoptoe and cause death. The number of lung-flukes may run from twenty to thirty or even higher. Healing is possible after death of the parasite.
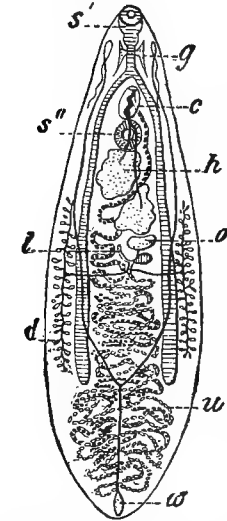
FIG. 500.—*Distoma lanceolatum.* (After Hertwig.) s^1, Anterior sucking-cup, and entrance into the forked intestine; s'', posterior sucking-cup; h, testicles with vasa deferentia; c, cirrus; u, uterus; o, ovary; l, duct of Laurer and shell-gland; d, yolk-stalks and duct leading to the shell-gland; w, water-vessel; g, ganglion. × 8.

Distoma felineum or *Distoma sibiricum* is a flat, almost transparent sucking-worm, of from 8-10 mm. in length and 1.5-2.5 mm. broad, which is present in the bile-passages of the cat and dog, and in a few countries (Siberia) has been observed in man. According to Winogradow it is the most common parasite in Tomsk. Askanazy observed several cases in Königsberg. The sources of the infection were fish eaten raw (roach, *Lenciscus rutilus*).

The inflammatory proliferations which the different forms of distoma cause in the liver of man, as well as in animals, may be followed by the development of carcinoma.

In **Distoma hæmatobium** or *Bilharzia hæmatobia* (Fig. 503) the two sexes are separate. The mouth and ventral cups lie close together on the tapering anterior extremity. In both sexes the sexual openings lie close behind the ventral sucking-cup. The male is 13-14 mm. long. The body is flat, but in its posterior portion is rolled together to form a tube (Fig. 503) which serves for the reception of the female.

The female is 16-19 mm. long and nearly cylindrical. The eggs are an elongated oval (Fig. 504), 0.12 mm. long, and possess a terminal or a lateral spine. According to observations by Sonsino, no alternation of
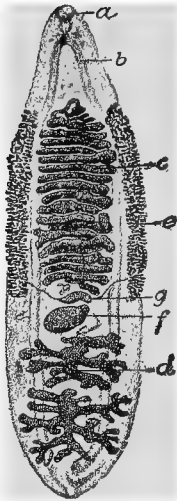
Fig. 501.   Fig. 502.

Fig. 501.—*Distoma spathulatum.* (After Katsurada.) *a*, Mouth sucking-cup; *b*, intestine; *c*, uterus; *d*, testicles; *e*, yolk-stalks; *f*, sperm-pouch; *g*, ovarium. × 6.
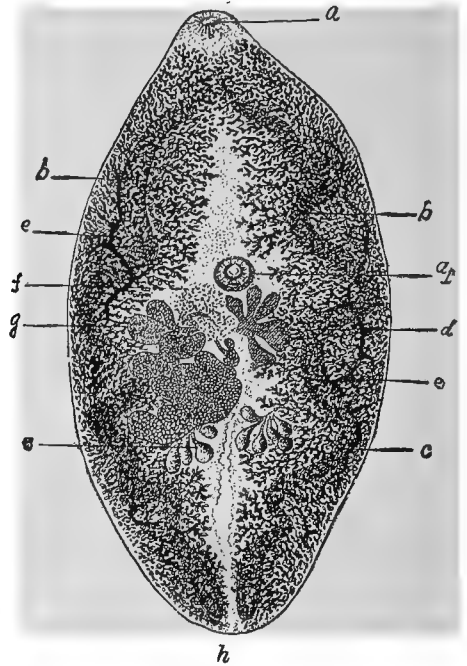
Fig. 502.—*Distoma Westermanni*, flattened by pressure, in the ventral position. (After Katsurada.) *a, a₁,* Mouth and abdominal sucking-cup respectively; *b*, intestinal loops; *c*, testicles; *d*, ovarium; *e*, yolk-stalks; *f*, shell-gland; *g*, uterus; *h*, excretory vessel. × 7.2.

generations occurs in the development of *Distoma Hæmatobium.* The part of intermediate host is taken by small crustacea, into which the ciliated embryo, swimming around in water, bores its way to become encapsulated in the tissues of its host. It is probable that infection may be transmitted through the drinking of water containing larvæ.

The worms are found in the trunk and branches of the portal vein, in the splenic vein, mesenteric veins, as well as in the vessels of the rectum and bladder; and may pass through the inferior mesenteric vein into the hæmorrhoidal and vesical veins, the veins of the ureter and prostate, and by chance into the inferior vena cava, and thence into the lungs. Their eggs are distributed, therefore, especially throughout the mucosa and submucosa of the ureters, bladder, and rectum, and occasionally

in the liver, lungs, kidneys, and prostate. While still in the urinary passages the cylindrical embryos (miracidia) covered with fine cilia may develop. Kartulis found them also in the skin of the leg and foot, and is of the opinion that the infection may take place not only through the intestine, but through the skin.

The deposit of eggs causes severe inflammations which lead to tissue-destruction and to proliferations of tissue, which appear in the mucous membranes as papillary and polypoid formations. In the bladder it may lead to incrustations and concretions, and to the development of fistulous tracts. In the liver the process leads to connective-tissue induration. Following the inflammatory process, development of carcinoma may take place in the bladder, seminal vesicles, prostate, and in the skin (Kartulis).
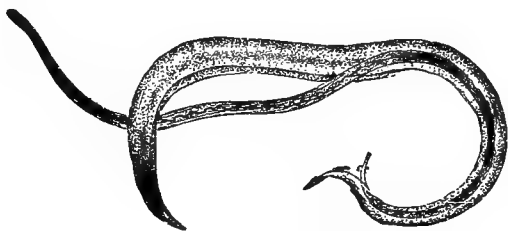
FIG. 503. FIG. 504.

FIG. 503.—*Distoma haematobium.* (After Leuckart.) Male and female, the latter lying in the canalis gynæcophorus of the former. × 10.

FIG. 504.—Eggs of *Distoma haematobium.* (After Leuckart.) *a*, Egg with terminal spine; *b*, egg with lateral spine. × 150.

The parasite is found along the entire eastern coast of Africa, and also in Zanzibar, Tunis, Lake Nyassa, in Beyrout, and in Sicily. It is most common in Egypt, where about twenty-five per cent. of the native population suffers from the disease.

2. *Cestoda (Tapeworms).*

§ 191. The **tapeworms** are *flat-worms devoid of mouth* or *intestine,* which increase after the method of alternate generation through the germination of a pear-shaped primary head or scolex, and remain united to the latter for a long time as a (usually) long, band-shaped colony. The single segments of this colony, the sexually active individuals, or **proglottides,** increase in size the more widely they become separated from their place of origin by the formation of new members, but outside of this are devoid of any distinguishing peculiarity. The pear-shaped **head** or **scolex,** on the other hand, is provided with from two to four suckers, and usually with curved claw-like hooks. With the aid of these clinging organs the tapeworms fasten themselves to the intestinal wall of their host, which appears to be invariably one of the vertebrate animals. The scolices develop from a round embryo having four to six hooks, and are found as the so-called " measles " in different organs, chiefly the parenchymatous ones, from which they pass by passive migration into the intestine of their future host.

The *tapeworms occurring as parasites in man* belong to different families: the *Tæniadæ* and the *Bothriocephalidæ.* The first occur in man as " measles " or tapeworms, the latter only as tapeworms.

§ 192. **Tænia solium** in its fully developed condition possesses a length of 2-3 meters. The head (Fig. 505) is the size of a small pin-head, spherical in form, with rather prominent sucking-cups. The crown of
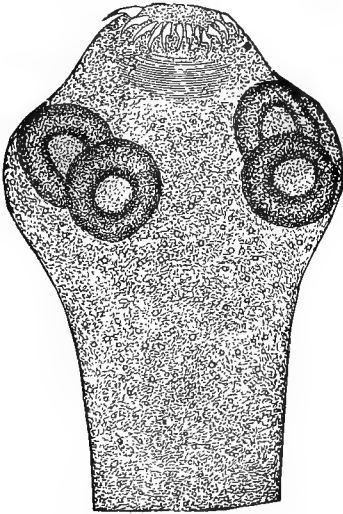
FIG. 505.   FIG. 506.   FIG. 507.

FIG. 505.—Head of *Taenia solium* with protruding rostellum (carmine, balsam). × 50.
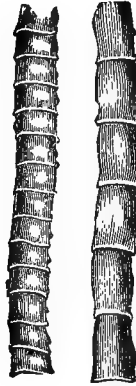
FIG. 506.—Half-developed and fully matured segments. Natural size. (After Leuckart.)

FIG. 507.—Two proglottides with uterus. (After Leuckart.) × 2.

the head is not infrequently pigmented and bears a fairly large rostellum with about twenty-six plump, close hooklets having short root-processes. Following the head there is a thread-like neck about an inch in length. At a certain distance from the head segmentation begins, the first segments being short, but their length increases with their distance from the head (Fig. 506); they become quadratic and finally longer than broad. The mature segments appear about 130 cm. behind the head, although the sexual organs are fully developed in earlier segments. The ripe segments (Fig. 507) are, when stretched out, 9-10 mm. long, and 6-7 mm. broad, and have rounded corners. The sexual opening is situated laterally just behind the mid-

FIG. 508.—Segment of *Taenia solium* with fully developed sexual apparatus. (After Sommer.) *A,* Surface view of segment; *B,* border of next anterior segment; *C,* that of next posterior segment; *a,* longitudinal excretory trunk; *a₁,* transverse anastomosis; *b,* longitudinal plasma-vessel; *c,* testicular vesicles; *d,* seminal ducts; *e,* vas deferens; *f,* cirrus-bag with cirrus; *g,* porus genitalis; *h,* border papilla; *i,* vagina; *k,* ovarium; *l,* albumin-gland; *m,* shell-gland, and oviduct in front of same; *n,* uterus.

dle of the segment. The uterus, which is filled with eggs, possesses seven to ten lateral branches separated from each other by a wide interval, and which break up into a varying number of boughs branching like a tree.

The parenchyma of the body of mature as well as of immature *proglottides,* or tapeworm segments (Fig. 508), is divided into two chief layers, the central one being designated the middle layer, the peripheral one the cortical layer. The middle layer contains the sexual apparatus (Fig. 508), *c, d, e, f, g, h, i, k, l, m, n*), as well as the water vascular system (*a*), an excretory apparatus, which traverses the whole tapeworm from the head to the last segment in the form of two canals lying in the lateral border of the middle layer. The canals are connected with each other at the posterior end of each segment (a^1) and also send out numerous fine, subdividing branches into the body-parenchyma.

The *sexual apparatus* consists of male and female sexual organs, which lie close together. A number of small, clear vesicles serve as testicles (*c*), they lie chiefly in the anterior portion of the middle layer. The vas deferens (*e*), which is connected with the testicles by the seminal ducts (*d*), empties into a grooved papilla situated on the lateral border (*h*). The coiled end (*f, g*) lies in a muscular bag and may be protruded through the sexual opening (*cirrus*). The female sexual opening lies close behind the male orifice in the same sexual cloaca. The vagina (*i*) leads thence to the posterior border of the segment. Before this is reached it widens into the seminal vesicle, and behind this into the fructifying canal and the so-called "globular body." The germ-preparing organs, which must be sought in the immature segments, consist of a double ovary (*k*) and a single albumin gland (*l*); these are sac-like or tubular organs lying in the posterior portion of the segment and communicating with the globular body. The latter is joined to the anteriorly located uterus (*n*), which at the time of sexual maturity forms a straight canal. When the eggs enter the uterus from the globular body, in which they pass their first stage of development, the above-mentioned lateral branches sprout and become filled with eggs. During this process the remaining sexual organs disappear.

FIG. 509. FIG. 510.

FIG. 509.—Eggs of *Taenia solium. b,* With primitive vitelline membrane; *a,* without primitive vitelline membrane. (After Leuckart.) × 300.

FIG. 510.—Cysticercus cellulosæ, with fully developed head *in situ.* (After Leuckart.) × 4.

The *cortical layer of the proglottides* is essentially muscular in nature, but in addition contains a number of so-called calcareous bodies, which are not entirely wanting in the middle layer as well. The musculature consists of smooth fibres, which form special groups in the suckers of the head. The surface of the tapeworm is covered with a clear cuticle, which forms the hooks on the heads.

The *eggs in the ovary* are thin-skinned, pale and yellow, nearly globular cells. In the uterus they change into yellow balls having a thick, more or less opaque shell, covered with closely set spicules (Fig. 509, *a*), and often surrounded by a second layer, an albuminous envelope (*b*) limited by a membrane; in it there are embedded granules (primitive vitelline membrane). The diameter of the eggs, not including the vitelline membrane, is about 0.03 mm.

The thick-shell spheres are not undeveloped eggs, but contain an embryo with six hooklets. Intra-uterine development of the embryo therefore takes place, the ripe segments are pregnant animals.

The *further development of the embryos* enclosed in the brownish shells takes place ordinarily in a new host. Should they gain access to the stomach of a *hog*, the egg-shell is dissolved, and the embryos, thus set free, penetrate into the stomach or intestinal wall. Thence they pass either by the blood-stream or by active migration through the tissues into different organs. Having reached a resting-place, the embryos undergo various metamorphoses and become changed in two or three months into a *cyst* filled with serum (Fig. 510), the inner wall of which shoots forth into a bud from which there develops a new tapeworm head, *scolex,* as well as a sac enclosing the same, *receptaculum scolicis.*

The cyst containing a tapeworm head is known as a **"measle"** or **cysticercus cellulosæ.** The scolices, when fully developed, possess a circle of hooklets, suckers, a water-vascular system and numerous calcareous bodies in their body-parenchyma. If they gain access to the human stomach, the cyst is dissolved, and there develops through the formation of segments from the scolex (*Amme*), a new chain of proglottides, a new *Tænia solium.*

The *Tænia solium inhabits the small intestine of man,* and is acquired by eating uncooked pork, since the "measles" belonging to this parasite occur almost exclusively in the hog and in man. By means of its sucking-cups and its circlet of hooks it clings firmly to the mucosa of the intestine; the remaining portions float in the intestine. Usually but a single parasite is present in the intestine, although several at the same time is not rare. Occasionally as many as thirty or forty have been observed in one individual. They excite irritation of the intestinal mucosa,

Fig. 511.—Cysticerci of the *Taenia solium,* in the epicardium and myocardium of a hog.

colic, and reflex disturbances of the central nervous system.

The "measles" occur in the tissues of the hog, sometimes singly, sometimes in great numbers (Fig. 511); individual organs, for example, a muscle or the heart, may be thickly studded with them.

In man, *cysticerci* occur in varied tissues — the muscles, brain, eyes, skin, etc. In the meninges and in the brain the measle may appear in the form of mulberry or grape-like collection of cysts, known as *cysticercus racemosus.* The cysts are for the greater part sterile, though some of them may contain a scolex.

The importance of the measle depends on its location, but is in general slight. Its presence in the brain often causes severe disturbances, but

in other cases all signs of disease may be lacking. Locally it excites slight inflammation, which leads to thickening of the connective tissue in its immediate neighborhood. The cyst may retain its vitality for years. After the death of the scolex the cyst contracts and there is deposited within it a chalky mass. The hooklets are preserved in this mass for a long time. Infection with the " measles " follows the introduction of eggs or proglottides into the stomach of man.

Tænia mediocanellata or **saginata** surpasses the *Tænia solium* not only in length, as it measures 4-7 metres and more, but also in its breadth and thickness, as well as in size of the proglottides (Fig. 512).

The *head* is devoid of rostellum and circle of hooklets (Fig. 513), has a flat crown and four large, powerful suckers, which are usually surrounded by a black border of pigment.

The *eggs* resemble those of *Tænia solium*. The fully developed pregnant *uterus* (Fig. 514) has a large number of lateral branches which run close to each other, and instead of branching dendritically divide dichotomously.
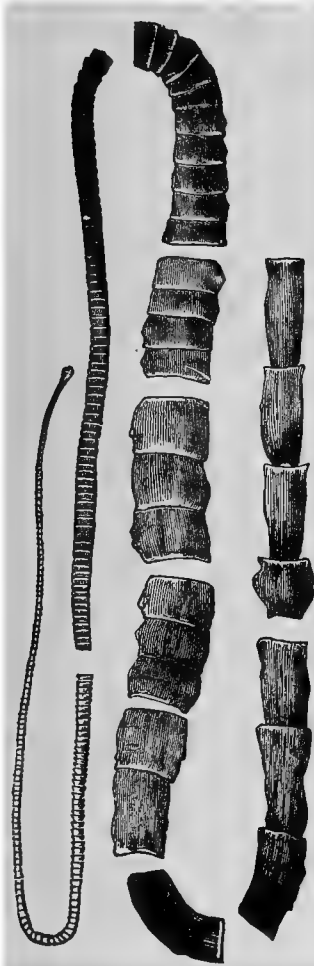
FIG. 512.　　　　　FIG. 513.　　　　　FIG. 514.

FIG. 512.—Portions of a *Taenia saginata*. (After Leuckart.) Natural size.
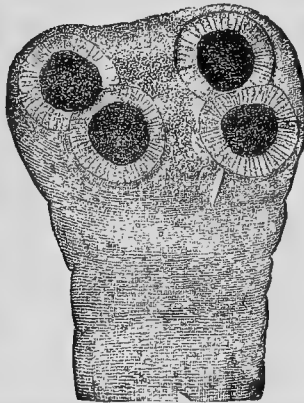
FIG. 513.—Head of *Taenia saginata*, retracted. Black pigmentation in and between the suckers. Unstained glycerin preparation. × 30.

FIG. 514.—Segment of *Taenia saginata*. (After Leuckart.) × ½.

The sexual opening lies back of the middle of the lateral border. The segments discharged spontaneously are for the greater part empty of eggs.

The " measles " are found usually in the muscles and the heart, more rarely in the other organs of *cattle* (*Cysticercus bovis*). They are somewhat smaller than the measles found in pork.

The *development* follows a course similar to that of *Tænia solium*. Malformations of this tapeworm are of frequent occurrence.

The parasite is acquired by man through eating raw beef. It has not been definitely settled whether the "measles" of this worm occur in man, but some authors (Arndt, Heller) believe that such an occurrence does take place.

By means of its powerful suckers the parasite is able to cling firmly to the intestinal wall. Stieda has observed a case in which a tænia 15 cm. long had penetrated the wall of the duodenum into the pancreas, and had caused tissue-necrosis and hæmorrhage in its neighborhood.

Tænia cucumerina or **elliptica** is 15–20 cm. long, and possesses a head with rostellum and circle of hooklets. It is of frequent occurrence in *dogs and cats,* but rare in man. Its cysticercoid inhabits the louse and flea of the dog, more rarely the flea of human beings (*Grassi*).

Tænia nana, a small tapeworm of from 8 to 15 mm. in length, has a head with four suckers and a circle of hooklets. It has been observed chiefly in Egypt and in Italy. *B. Grassi* was able to obtain several thousands of specimens from two Sicilians who had suffered from severe nervous disturbances. According to his investigations, the tænia passes its entire development, from the embryo on, in the same host. *Visconti* (Rendiconti R. Instituto Lombardo, xviii., 1886) found, at the autopsy of a young man from northern Italy, great numbers of *Tænia nana* in the lower portion of the ileum. In Germany it has been observed in only a few cases (*Mertens, Leichtenstern, Röder*).

Tænia diminuta (Rud.) or *flavopuncta* (*Weinland*), *minima* (*Grassi*) is a tapeworm, 20–60 mm. long, and has a head without hooklets. It is of common occurrence in rats and mice, and has been observed in a few cases in man. According to *Grassi* and *Rovelli,* the measles live in a small butterfly, as well as in beetles.

Von Linstow has described as **Tænia africana** a large tapeworm with scolex devoid of hooklets, which he observed among the negroes of German East Africa.

Besides those which also occur in man, tæniæ are of frequent occurrence in **domestic animals,** both in the carnivora and in birds, as well as in the herbivora.

Tænia marginata of the dog is a tapeworm, 1–5 m. long, provided with a double circle of hooklets. Its cysticercus forms cysts (*cysticercus tenuicollis*) of varying size in and under the serous membranes of sheep, cattle, goats, and hogs.

Tænia serrata is found in the dog. It is 50–100 cm. long, and possesses a circle of hooklets. The cysticerci (*cysticercus pisiformis*) are found in rabbits and hares.

Tænia cœnurus is a tapeworm of the dog, 40–100 cm. long, and is provided with hooklets. It passes its cystic stage most frequently in sheep, where it seeks the central nervous system and forms cysts varying in size from a millet seed to that of a hen's egg, that contain great numbers of scolices. Its presence in the brain (*cœnurus cerebralis*) gives rise to the so-called "staggers" of sheep.

FIG. 515.— Full - grown Tænia echinococcus. (After Leuckart.) × 12.

§ 193. The **Tænia echinococcus** lives in the intestinal canal of the dog. It is 4-5 mm. long and possesses only four segments, the most posterior of these surpassing in length all the rest put together (Fig. 515).

The small hooklets have coarse root processes and are implanted on a rather bulging rostellum. Their number runs from about thirty to fifty.

The **cyst-worm (hydatid)** alone is found in man. It results from the introduction of tænia eggs into the intestinal canal.

If the embryo wanders from the intestinal canal into an organ, it changes into a *cyst,* which is not capable of active motion. It consists of

an outer *lamellated,* elastic *cuticle* (Fig. 516, *a*) and a parenchymatous layer (*b*) lying internal to this, consisting of granular masses and cells, and containing muscle-fibres and a vascular system. When the cyst has reached the size of a walnut (sometimes earlier), there are formed from the parenchymatous layer small *brood-capsules* (*c*) which produce a great number of *scolices.* The first stage of these tapeworm heads consists of coarsely granular protoplasmic masses (*d*) lying in the wall of the brood-capsule; these develop further and show cavities (*e*) communicating with the cavity of the brood-capsule, and later become differentiated into a tapeworm head (*f*) furnished with a circle of hooklets. The head (*h*), which now protrudes into the lumen of the brood-capsule, (*g, h*) is about 0.3 mm. long, possesses a rostellum with small, plump hooklets, four suckers, a water-vascular system, and numerous chalky
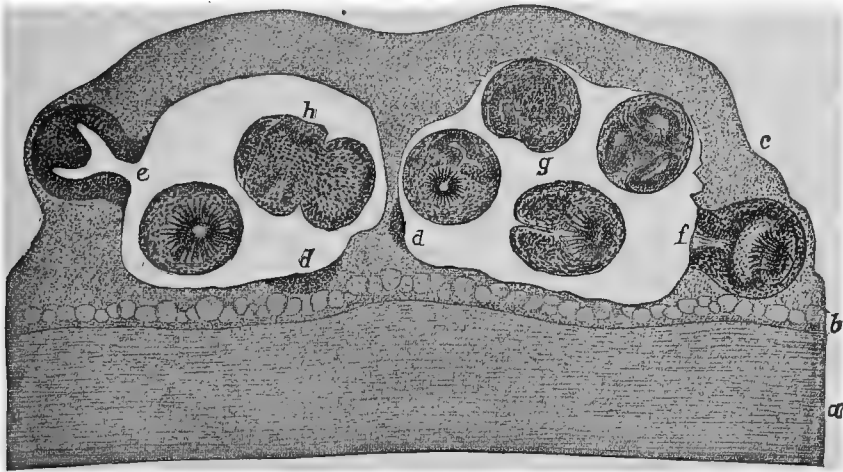
FIG. 516.—Wall of an echinococcus-cyst containing brood-capsules and scolices (alcohol, carmine). *a,* Chitinous membrane; *b,* parenchymatous layer with vesicular cells; *c,* brood-capsules; *d, e, f, g, h,* scolices in different stages of development. × 100.

bodies 'in it's parenchyma. Frequently the anterior part of the body is telescoped into the posterior (*g*).

In many cases the **echinococcus cyst remains single.** Its only change consists in enlargement to the size of an orange or fist, through the formation of new brood-capsules and heads. The surrounding tissue forms a capsule, in which the cuticular cyst lies. The cavity of the cyst is filled with clear fluid, which does not coagulate on boiling or on the addition of acids, and contains none or but little albumen, but does contain sodium chloride, calcium oxalate, triple phosphates, uric acid, sugar (in the liver), and often cholesterin. The brood-capsules are always situated on the inner surface, if not mechanically dislodged; and are visible through the transparent parenchyma as small white points. Occasionally the cyst remains sterile.

In many cases **daughter-cysts** (Fig. 517, *c*) are formed. Their development proceeds in the depth of the cuticle independently of the real parenchymatous layer. Between two lamellæ of the cuticle there arises a collection of granules, which surround themselves with a cuticle, and thereby become the centre of a new set of layers. As the number

of layers increases, the cavity grows larger and the contents become clear. If the daughter-cysts grow they bulge out the wall of the mother-cyst like a hernial sac, until it finally gives way and liberates its contents. If they now pass outward by the side of the parent-cyst, they obtain from the parenchyma in which they lie an external capsule of connective tissue, and then produce brood capsules in the same manner as the primary cysts arising from the six-hooked embryos.

An echinococcus with *exogenous proliferation* is called **echinococcus granulosus, or sometimes echinococcus veterinorum** from the fact that it is of frequent occurrence among domestic animals.
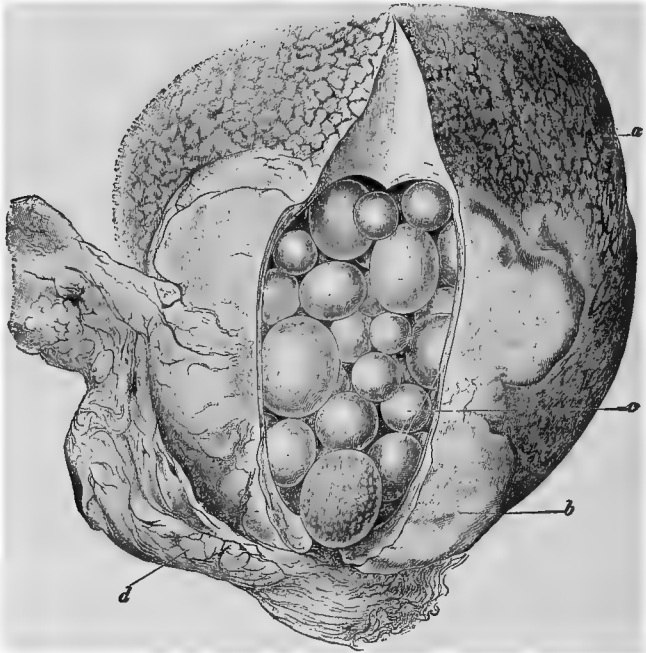
Fig. 517.—*Echinococcus hydatidosus.* *a,* Surface of liver; *b,* indurated connective tissue; *c,* daughter-cysts within a parent-cyst, which has been opened by an incision; *d,* adhesions. Three-fifths natural size.

A second compound form of echinococcus is the **echinococcus hydati-dosus.** It is characterized by the presence of inner *daughter-cysts* (Fig. 517, *c*). According to statements by Naunyn, and confirmed by Leuckart, the scolices and brood-capsules undergo cystic metamorphosis, and so become changed into daughter-cysts which occasionally produce grand-daughter cysts. Through the formation of numerous daughter-cysts the chief cyst may attain large size.

Infection of man follows the ingestion of the eggs of the tænia which occurs in dogs. The cysts are most often found in the liver, but the echinococcus occasionally occurs in the lungs, spleen, kidneys, intestine, in a bone or in the heart. With the exception of the disturbance from pressure and of the local inflammation which it causes (the latter leading to the formation of a connective-tissue capsule in many organs) the cyst produces no harmful effects. It often dies on attaining a certain size

(that of a walnut to an apple), the fluid is absorbed, the cyst contracts, and there remains in it fatty, cheesy detritus, which often calcifies. The hooklets are preserved for a long time.

In other cases the echinococcus becomes larger, particularly when endogenous or exogenous daughter-cysts develop. It may become dangerous through size alone. Severe inflammations are occasionally produced, particularly after trauma, or after rupture of the cyst into one of the body cavities. Rupture into a blood vessel may occur and lead to the metastasis of cysts and embolic blocking of vessels. In more favorable cases rupture may take place externally or into the intestines.

The spontaneous spread of brood-capsules and scolices in the same host, as well as the experimental transplantation of the same into another host, may lead to the formation of new cysts.

The form known as **echinococcus alveolaris** or **multilocularis** pre-
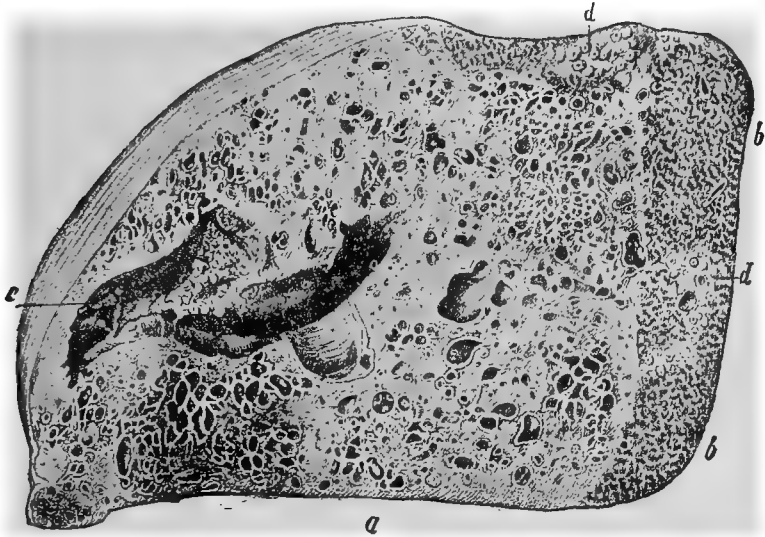
FIG. 518.—Transverse section of an *Echinococcus multilocularis*. *a*, Alveolar echinococcus tissue; *b*, liver tissue; *c*, cavity produced by softening; *d*, fresh nodules. Natural size.

sents itself as a hard tumor, situated usually in the liver, rarely in other organs (brain, spleen, adrenal), and possesses an alveolar structure (Fig. 518), in that a firm, dense connective-tissue mass encloses numerous cavities. Its contents are translucent and gelatinous, or consist of fluid and a gelatinous substance. The cavities are spherical or irregular in shape. Usually, through softening and disintegration of the parenchyma, ulcerative cavities (*c*) are formed. In other places the tissue is fibrocaseous, necrotic or calcified, or impregnated with bile. At times caseation of the proliferating tissue is the most prominent feature of the process; at other times the alveolar structure. When the development of the colonies has progressed further, there appear in the tissue gray and yellowish nodules (*d*) in which cavities containing colloid plugs (chitincysts and coils) are developed. The exquisite alveolar structure gave rise to the now abandoned theory that this form of echinococcus is an alveolar, colloid-containing tumor of the liver. Virchow first recognized the true

nature of the condition, and demonstrated that the so-called colloid masses were echinococcus cysts.

According to the investigations of Melnikow-Raswedenkow the alveolar echinococcus is to be regarded as a different species, which increases in the tissue of the host in a peculiar manner, suggesting the mode of development of the Trematodes; and in many cases spreads by hæmatogenous and lymphogenous metastases from the primary focus of development to other organs (lymph-nodes, lungs, brain).

Should the alveolar echinococcus occurring in any organ, for example, in the liver, encroach on neighboring tissues, there are found in the latter finely granular multinucleated protoplasmic structures surrounded by granulation tissue. Later, small chitinous cysts develop or a folded membrane studded with granular masses, while the granulation tissue becomes changed into fibrous connective tissue. The majority of the cysts remain sterile. Scolices develop only in a few. Ovoid granular structures with a thin membrane may be formed, and are regarded by Melnikow as embryos. The chitinous membranes which lie in the granulation tissue are often surrounded by giant-cells.

The life-history of the alveolar echinococcus outside the parenchyma of the organ is unknown; feeding to dogs has given no positive results. It appears that the embryos and scolices are not capable of development in the intestine of the dog.

The ordinary echinococcus is widely distributed, though not common. It is of most frequent occurrence in Iceland, where the inhabitants live in close association with dogs. The alveolar echinococcus has been observed chiefly in Switzerland, South Germany, Austria, and in Russia.

§ 194. **Bothriocephalus latus** or **pithead** is the most formidable tapeworm of man, measuring 5-8 metres in length, and consisting of three to four thousand short but broad segments (Fig. 519), which are broadest in the middle region and narrower at the end. The length of the largest segment is about 3.5 mm., the breadth about 10-12 mm.

The head (Fig. 520) has a long oval or club shape, is about 2.5 mm. long and 1 mm. broad. It is somewhat flattened, possesses on each margin a slit-like depression and is mounted on a filiform neck.
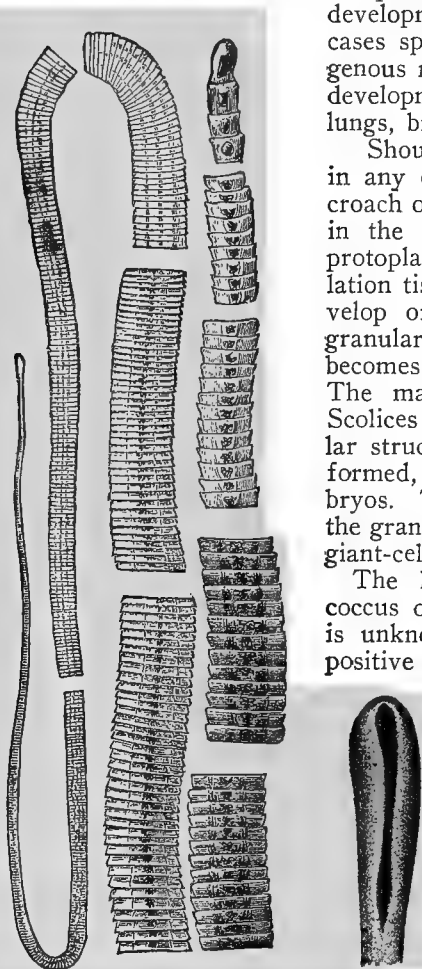
FIG. 519.   FIG. 520.

FIG. 519.—*Bothriocephalus latus.* (After Leuckart.) Natural size.

FIG. 520.—Head of *Bothriocephalus latus* of Bremser. (After Heller.) Enlarged.

The body is thin and flat like a ribbon, with the exception of the central parts of the segments, which project somewhat outward. At this spot the uterus is found, in the shape of a single canal, which forms a number of coils (Fig. 521, *m*). When the eggs collect here in great numbers the lateral coils of the uterus arrange themselves in folds, so that a remarkable rosette-like appearance is produced. The sexual openings lie in the middle line of the ventral surface, near the anterior border of the segment, the female orifice (*o*) being close behind the male opening (*f*).

The ovary (*g*) is a double organ which lies in the middle layer; the yolk-chambers (*h*), on the other hand, are located in the cortical layer.
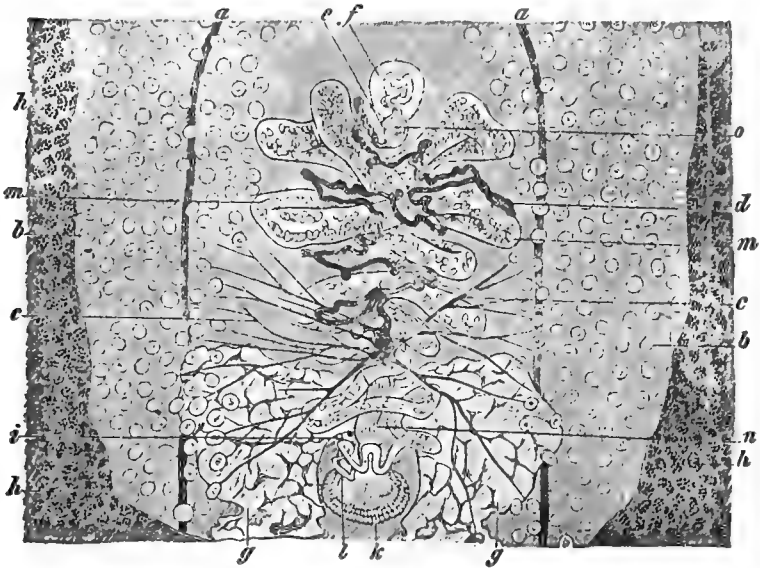
FIG. 521.—Median portion of a proglottis of *Bothriocephalus latus*, seen from the dorsal surface. The cortical layer of the segment has been removed except a border on each side, and the middle layer thus exposed. (After Sommer.) *a*, Lateral vessels; *b*, testicular vesicles; *c*, testicular canaliculi; *d*, seminal ducts; *e*, posterior, *f*, anterior hollow-muscle apparatus (cirrus-sac of vas deferens); *g*, ovary; *h*, yolk-chambers lying in the cortical area; *i*, collecting-duct of yolk-stalk, branches of which lead ventrally to the yolk-chambers; *k*, shell-gland; *l*, beginning of the uterus; *m*, loop of uterus filled with eggs, the orifice of uterus opening on the anterior surface; *n*, vagina; *o*, vaginal opening. × 35.

The shell-gland (*k*) lies behind the collecting-tube (*i*) of the yolk-chambers. The testicles consist of clear vesicles (*b*) which lie in the lateral portions of the middle layer, and communicate by means of fine canals (*c*) with the vas deferens (*d*), which terminates in the cirrus-sac (*e*, *f*).

The *eggs* (Fig. 522) are oval, and about 0.07 mm. long and 0.045 mm. broad. They are surrounded by a thin, brown shell, the anterior pole of which forms a sharply outlined cap-like cover.

The *Bothriocephalus latus* occurs chiefly in Switzerland, in the northeastern parts of Europe, in Holland and in Japan, and lives, as does the Tænia, in the small intestine of man. According to Bollinger it is rather frequent in Munich. The first stage of development of the eggs takes place in water. After the lapse of months there develops an embryo (*Oncosphæra*) armed with six hooklets and covered with ciliæ (Fig. 523). This

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develops, in some intermediate host as yet unknown, into a measle (*Plerocercoid*), which, according to the investigations of Braun in the Russian Baltic provinces, seeks out as second intermediate host the pike or tadpole, and develops in the muscle or internal organs of these animals into a sexless tapeworm. According to Grassi and Parona, the measle of Bothriocephalus latus in Italy occurs in the pike and in the river-perch. In Japan it is found most frequently in the *Onchorhynchus Perry* (Ijima, Leuckart). Zschokke found it in the Lake of Geneva in the following forms of fish: *Lota vulgaris, Perca fluviatilis, Salmo umbla, Esox lucius, Trutta vulgaris* and *Trutta lacustris*. It is found most often in the tadpole (*Lota vulgaris*) and perch (*Perca fluviatilis*). Should the measle gain entrance, through ingestion of the fish mentioned, into the intestinal canal of man, it again attains sexual maturity. According to Braun and Parona the measles may also be brought to development in both dogs and cats. The presence of Bothriocephalus in the intestine gives rise to a gradually increasing anæmia, which resembles pernicious anæmia. The diminution of the red blood-cells and of the hæmoglobin content of the blood is probably due to the fact that, after the death of the tapeworm, poisonous products arise having an injurious action on the blood-corpuscles.
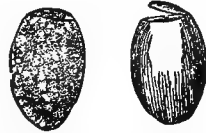
FIG. 522.

FIG. 523.

FIG. 522.—Eggs of *Bothriocephalus latus*, the one at the right having been emptied of its yolk-contents. (After Leuckart.)
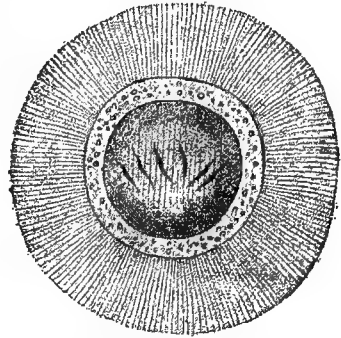
FIG. 523.—Free embryo of *Bothriocephalus latus* with ciliated envelope. (After Leuckart.)

Bothriocephalus cordatus (Leuckart) is a tapeworm, of 80–115 cm. long, and has a heart-shaped head, whose sucking-grooves are flattened. The breadth of the ripe segments is about 7–8 mm.; the length, about 3–4 mm. In Greenland and Iceland it is a frequent parasite of the dog, seal, and walrus, and is found occasionally in man. The measles likewise occur in fishes.

Bothriocephalus Mansoni (*Cobbold*) or *liguloides* (Leuckart) is the measle (plerocercoid) of a tapeworm which has been observed a few times (Manson, Ijima, Murata) in the body-tissues and in the descending urinary passages or in the urine. Its origin is not known.

Bothriocephalus felis, which occurs in cats, is similar to Bothriocephalus latus.

Bothriocephalus latus occurs also in dogs. In the United States this worm is found occasionally in individuals who have come from various infected regions of Europe. In the mining regions of Northern Michigan it has been found a number of times in Finns.

B. NEMATHELMINTHES (ROUND WORMS).

§ 195. All the **round worms** which occur as parasites belong to the **Nematoda.** They possess a slender, cylindrical, elongated, at times filiform body without segments or appendages. The cuticle is thick and elastic. The mouth opening is found at one extremity, and is provided sometimes with soft and sometimes with horn-like lips. The elongated intestine, together with the pharynx and chyle-stomach, extends through

FIG. 524. FIG. 525.

FIG. 524.—*Ascaris lumbricoides.*
(After Perls.) *A,* Female; *B,* male.
Natural size. At *a* is the female
sexual orifice; *c,* the two spicules of the
male; *b,* the (enlarged) cephalic end with
the three lips.

FIG. 525.—Egg of *Ascaris lumbricoides,*
with shell and albuminous covering.
(After Leuckart.) × 300.

the entire body-cavity (Fig. 524) and opens on the ventral surface a short distance from the posterior extremity, which is usually awl-shaped. The sexual organs and their openings are also found on the ventral surface. The female sexual orifice is located at about the middle of the body, less frequently near the anterior or posterior extremity (Fig. 524, *A, a*). In the male the sexual opening and the anus are together (*B, c*). The chitinous covering of the lower gut forms in the male the means of clinging during the act of copulation. The males are usually smaller than the females. The development is direct, and the metamorphoses are not striking. The nematodes occurring in man are in part harmless parasites of the intestine, and in part dangerous, sometimes even fatal.

§ 196. **Ascaris lumbricoides,** the common round-worm (Fig. 524) is a light-brown or reddish, cylindrical worm with tapering ends. The female (*A*) is 25-40 cm. long, the male (*B*) is much smaller, and the posterior extremity of the latter is bent in the form of a hook and provided with two spicules (*c*) or chitin processes.

The mouth (*b*) is surrounded by three muscular lips bearing fine teeth. The female sexual opening (*A, a*) lies anterior to the middle of the body. The eggs which the mature female carries in enormous number possess in their fully developed condition a double shell (Fig. 525) and around this an albuminous envelope. They are about 50–70 μ in length. The worm inhabits the intestinal tract, most frequently the small intestine. It is the most common parasite of man, and is frequently found in great numbers. When mature females are present the fæces contain the eggs in abundance. These are resistant to external influences, for example to drying and freezing.

The eggs require no intermediate host (Lutz, Leukart, Grassi, Epstein). Man is infected by the ingestion of eggs which have been expelled from the bowel and have matured in the fæces.

According to feeding-experiments which Epstein carried out on human be-ings with eggs which had been cultivated in damp fæces for a long time, the round-worm attains its maturity in from ten to twelve weeks after the ingestion of the eggs. At this time the male is 13–15 cm. long, and the female from 20–30 cm. Their presence in the intestine may not cause any noticeable disturbance. When present in large numbers they sometimes, especially in children, cause intestinal catarrh, vomiting, nervous disturbances and convulsions. Occasionally the worm crawls into normal and pathological openings in the wall of the intestinal canal, and in this way causes trouble. Thus, when it crawls into the ductus choledochus, it may produce bile-stasis. If it penetrates an ulcer into the peritoneal cavity or into a hernia sac, it may excite inflammation of the tissues concerned. According to Leuckart it may penetrate the un-injured intestinal wall. It is frequently passed with the stools, but at times *per os* in vomiting. From the pharynx it may wander into the larynx.

According to *Crowell,* the dangers of *ascariasis* are apt to be under-estimated. The worms may cause symptoms and even death through toxic, reflex and mechani-cal effects either in the larval stage, or while adult in the intestine, or in the course of migration to other parts of the body. The number of worms in the intestine varies from one or two to hundreds, occasionally producing symptoms of intes-tinal obstruction. Collections of worms in the sigmoid may cause palpable masses simulating tumor growth and the abdomen has actually been opened under this misconception. The worm is often found in the peritoneal cavity as a result of escape through any available exit, or by direct passage through the intestinal wall by separation of its fibers which, coming together again, leave no trace of perfora-tion. Sometimes the worm escapes through the umbilicus or from fistulous tracts in the groin or urethra. In countries where the parasite abounds, the worm not infrequently opens repaired wounds of the intestine with the production of fatal peritonitis. Migration of the ascaris into the common bile duct; gall-bladder, intrahepatic and pancreatic ducts is common. In this way severe infections of these passages arise. It may also invade the accessory nasal sinuses, the antrum of High-more, the lachrymal duct, Eustachian tube, larynx and trachea. The reproduction of ascariasis in animals and in man is often associated with the occurrence of broncho-pneumonia due to the presence of larvæ in the respiratory passages. Crowell suggests that, in certain tropical countries, broncho-pneumonia in infants and children may not uncommonly be due to the same cause. Clinical observations and the therapeutic effects of vermifuges unite to incriminate the ascaris as the cause of all sorts of toxic and nervous phenomena — fevers, nausea, flatulence, abdominal pains, convulsions, tetany, symptoms of chorea, hysteria and epilepsy, psychic disturbances, symptoms simulating meningitis, and many other disorders of similar nature. The disturbances of the central nervous system are attributable to chronic poisoning by volatile aldehydes of fatty acids, Flury having found these and other pharmacologically active substances both in the body and in the excretions of pig-ascaris. In this climate, ascaris is not uncommon. At Bellevue Hospital we meet with the worm in the intestine in about 5 per cent. of all autopsies, particu-larly in Europeans. In the Philippine Islands, on the contrary, infestation with ascaris was demonstrated by Willets in 62.3 per cent. of nearly 20,000 persons. (Crowell, American Journal of Medical Sciences, 1920; Flury, Arch. f. exp. Path. u. Pharm., 1912; Willets, Philippine Journal of Science, Section B, 1911.)

In domestic animals ascarides are of frequent occurrence. *Ascaris lumbri-coides* is found in swine (*Ascaris suilla*) and in cattle (*Ascaris vituli*). *Ascaris megalocephala,* a round worm whose female is 18–37 cm. long, is a common para-site of the horse and donkey. *Ascaris mystax,* whose female reaches a length of 12 cm., is found frequently in dogs and cats, and has also been observed in man. Various species, designated as *Heterakis,* occur in birds. Heterakis maculosa, the round worm of pigeons, may cause the death of the pigeon when occurring in large numbers in its intestine.

§ 197. **Oxyuris vermicularis**, *awl-tail*, *pinworm*, or *threadworm* is a small round worms (Fig. 526), the female being about 10 mm. long (*a, b*)

and pointed at the caudal extremity like an awl, while the male is about 4 mm. long (*c*) with a blunt posterior end, the anus being provided with a spiculum.

The eggs (Fig. 527, *a*), which the body of the female often contains in great numbers, are 50 μ long and 24 μ broad, have a flat and a curved surface, and a shell which is covered by a thin albuminous layer. *Oxyuris vermicularis* inhabits the large intestine and the lower portion of the small intestine. According to Zenker and Heller only the impregnated mature females are found in the large intestine, the young individuals and the males remain in the small intestine. They occur frequently in larger or smaller numbers. At night they often wander from the rectum over the anal region, and may enter the vagina; they excite itching of the affected parts. In the pelvic peritoneum encapsulated worms or eggs have been observed a number of times. It has not been determined whether they can penetrate the intestinal wall (Vuillemin). Wagener found dead and calcified worms in the submucosa of the intestine.

For the development of the eggs (Fig. 527, *a-e*), it is necessary after their expulsion with the fæces that they again be taken into the stomach of man or beast. It is probable that the original host may again infect himself with oxyuris, for example, the eggs becoming attached to his finger during the act of scratching may later get into his mouth.

FIG. 526.—*Oxyuris vermicularis.* *a*, Sexually mature female; *b*, female full of eggs; *c*, male. (After Heller.) × 10.

FIG. 527.—Eggs of *Oxyuris vermicularis* in different stages of development. (After Zenker and Heller.) *a*, *b*, *c*, Segmentation of yolk; *d*, tadpole-shaped embryo; *e*, worm-shaped embryo. × 250.

The eggs are resistant to drying, and in this condition may be widely scattered.

Oxyuris is a common inhabitant of the appendix and sometimes gives rise to grave symptoms. *Brumpt*, in Paris, found pin worms in the appendix in 3.5 per cent. of normal cases and in 40 per cent. of all cases of appendicitis. *Hoepfl*, in Germany, demonstrated them in the appendix in 21 per cent. of all cases of appen-

FIG. 528.

FIG. 529.

FIG. 530.
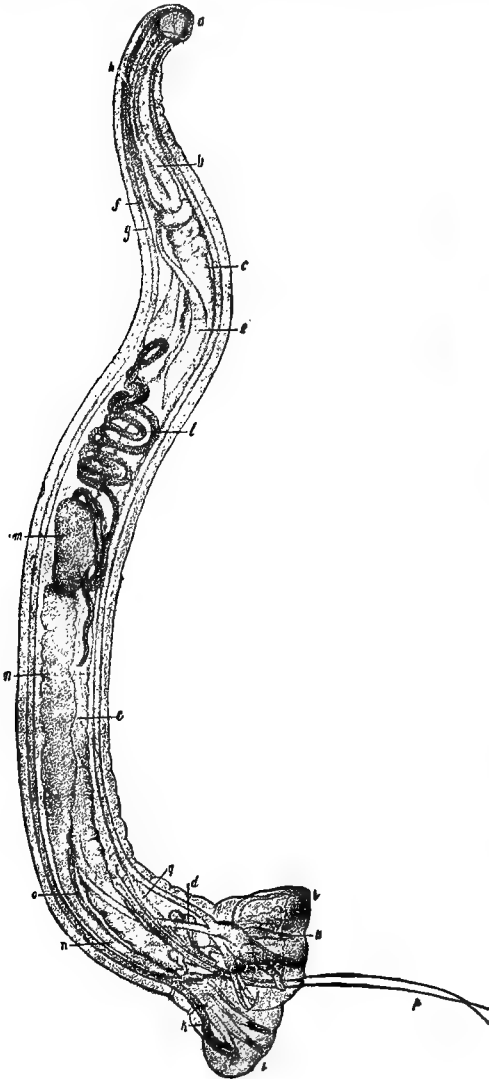
FIG. 528.—Male of *Anchylostoma duodenale*. (After Schulthess.) *a*, Head with mouth-capsule; *b*, œsophagus; *c*, intestine; *d*, anal-glands; *e*, cervical glands; *f*, skin; *g*, muscle-layer; *h*, porus excretorius; *i*, three-lobed bursa; *k*, ribs of the bursa; *l*, testicular canal; *m*, seminal vesicle; *n*, ejaculatory duct; *o*, groove of latter; *p*, penis; *q*, penis sheath. × 18.

FIG. 529.—Cephalic end of *Anchylostoma duodenale*. (After Schulthess.) *a*, Mouth-capsule; *b*, teeth of ventral border; *c*, teeth of dorsal border; *d*, mouth cavity; *e*, skin protuberance on ventral side of head; *f*, muscular layer; *g*, dorsal groove; *h*, œsophagus. × 100.

FIG. 530.—Eggs of *Anchylostoma duodenale*. (After Perroncito and Schulthess.) *a-d*, Different stages of segmentation; *e*, *f*, eggs with embryos. × 200.
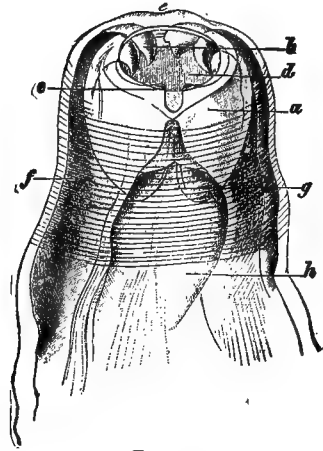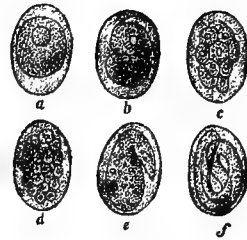
dicitis. In London, *Still* found oxyuris in 19 per cent. of all normal childrens' appendices examined at autopsy. In this country, *Cecil* and *Bulkley* found oxyuris in 13 per cent. of 129 cases of appendicitis in children. The oxyuris burrows into the submucosal tissues and its invasion is usually accompanied by extravasation of blood and sometimes by the formation of hæmorrhagic ulcers of the mucosa. A characteristic feature of the lesions is absence of inflammatory reaction about them, except in those cases where there is secondary bacterial infection. In some instances the process may heal spontaneously. (Journal Experimental Medicine, 1912.)

§ 198. **Anchylostoma duodenale** (*Dochmius duodenalis,* or *Strongylus duodenalis, Uncinaria duodenalis, Uncinaria Americana* [*Stiles*], Hook-worm, is a small worm belonging to the family of *Strongylides,* which inhabits the upper part of the small intestine (Fig. 528). The cylindrical body of the female is 5–18 mm. long, that of the male 6–10 mm. The cephalic end (Fig. 529) is curved toward the dorsal surface, and possesses a bellied mouth-capsule (*d*). It is almost completely divided dorsally, and the cleft is covered by two chitinous lamellæ. On the ventral border there are four incurving teeth (*b*), on the dorsal border two teeth which are perpendicularly placed (*c*), all being held together by chitinous bands.

The male is provided at its caudal extremity with a threefold bursa (Fig. 528, *i*) and two thin, fishbone-like spicules (*p*). In the female the posterior end is pointed, and bears an awl-shaped spine; the vulva lies posterior to the body centre. The oval eggs (Fig. 530) are 44–67 μ long, 23–40 μ broad. They undergo the first stages of cleavage in the human intestine (*a–d*), develop further in muddy water (*e, f*), and may then, if brought into the human intestinal tract, develop into sexually mature animals. With its teeth the worm works its way into the mucous membrane as far as the submucosa, and sucks itself full of blood. Its point of attack is distinguishable later by a small ecchymosis in the middle of which there is a white spot with a central perforation. Occasionally there are found in the intestinal mucosa small cavities filled with blood, in each of which there lies a coiled-up worm. The parasites, when present in large numbers, cause continuous and serious loss of blood, which may lead to severe forms of anæmia (*Egyptian chlorosis*), but they are not infrequently found in individuals who present no symptoms of disease. The parasite is common in the tropics, also in Japan. According to Griesinger and Bilharz about one-quarter of the native Egyptians suffer from this disease. The parasite was often observed in the workmen engaged in the Saint Gotthard tunnel. According to Menche and Leichtenstern the brickfields of the Rhine provinces are to a great extent infected with anchylostoma (brick-burner's anæmia).

In 1903 the worm was distributed to an extraordinary degree throughout the mines of the district of Dortmund, so that in the autumn of that year over seventeen hundred individuals infected with the worm were found.

The infection takes place chiefly through larvæ ingested with the drinking-water and food. According to the investigations of Looss and Schaudinn, the larvæ may penetrate through the skin into the veins, thence are carried into the lungs, whence they wander through the bronchi, trachea, and larynx and into the intestinal tract. In experiments made on apes the larvæ may be found in the intestine within twenty-four hours.

According to *Stiles* (1902), the hookworm disease of the American continent is due to a species distinct from that found in Europe. He distinguishes them as the Old-World hookworm and the New-World hookworm (*Necator americanus* or *Uncinaria americana*). The latter form is prevalent throughout the Southern United States as far north as the Potomac River, and in the West Indies, and has also been found in Italy, Africa, China, and the Philippines. It is a cylindrical worm 7-11 mm. long, with a dorsal and ventral pair of lips, a prominent dorso-median buccal tooth, and four buccal lancets. In the male the dorsal ray of the bursa divides at the base and each branch possesses two tips. In the female the vulva is in the anterior half of the body. The eggs have more sharply rounded poles than those of the Old-World worm. It is estimated that about ninety per cent of the rural population of Porto Rico is infected with this parasite, and in some parts of Florida a similar degree of infection is reported. According to *Stiles*, the piney-wood and sandy-soil portions of the South are especially regions of infection. In these regions "ground itch" is of common occurrence, and is believed to be due to the penetration into the skin of the larvæ of the hookworm. Among the most striking symptoms of the American infection are anæmia, perverted appetite ("clay-eaters"), pain and tenderness in the epigastrium, delayed puberty, mental lassitude, etc. The "cotton-mill anæmia" of the South is due to a moderate degree of hookworm infection. The economic importance of uncinariasis in America is great. It is estimated that thirty per cent of all deaths in Porto Rico are the result of hookworm infection. According to *Stiles*, this infection is chiefly responsible for the inferior mental and physical condition of the poorer classes of whites in certain parts of the Southern States.

Eustrongylus gigas, a palisade-worm of red color, whose female reaches a length of 1 metre, is a rare parasite, which has been observed a few times in the kidney-pelvis of man. It occurs frequently in dogs. It possesses a mouth-opening with six papillæ; the male has on its posterior extremity a bursa with a single spiculum. The eggs are oval, 0.06 mm. long, and provided with a rough albuminous capsule.

Strongylus longevaginatus, a thread-like, white worm, 26 mm. long, was once observed in the lung of a boy.

In the **domestic animals** *Strongylides* occur in greater numbers than in man, and are in part inhabitants of the intestine, and in part of the lungs (*Müller*, "Die Nematoden der Säugerthierlungen," *Deut. Zeitschr. f. Thiermed.*, xv., 1886).

Dochmius trigonocephalus and *Dochmius stenocephalus* occur in the intestine of dogs, and give rise to anæmia similar to that produced by the Anchylostoma in man.

Strongylus armatus is a common parasite of the horse, which enters the intestinal tract as an embryo, bores into the intestinal wall (*Olt*), thence into the liver, by way of the portal vein, and into the lungs and organs of the major circulation. Following this migration, it may develop in diverse organs and cause the formation of fibrous nodules, which become calcified after the death of the parasite enclosed in them. In the intestinal wall it may develop after direct migration or after embolic lodgment in the part, and leads to the formation of cavities, from which it again breaks through into the intestinal lumen. In the mesenteric arteries it attains sexual maturity, and causes thrombosis and the formation of aneurisms. The male of the mature worm is 20-30 mm. long; the female, 20-55 mm.

Strongylus tetracanthus, which inhabits the large intestine of the horse, causes hæmorrhagic enteritis in large numbers.

Strongylus paradoxus is an extremely common parasite of the lungs of hogs. *Strongylus capillaris*, *Str. commutatus*, and *Str. filaria* are frequent parasites of the lungs of goats and sheep, and different species may be present in the same lung at one time (*Schlegel*, "Die durch Strong. capillaris verursachte Lungenwurmseuche der Ziege," *Arch. f. wiss. Thierheil.*, 25 Bd., 1899). The latter causes in sheep bronchitis and nodular proliferating pulmonary inflammations; through the swallowing of many embryos inflammations of the intestine may be produced.

Strongylus rufescens and *Str. paradoxus*, *Nematoidium ovis pulmonalis* (*Lydtin*), or *Pseudalius ovis pulmonalis* (*Koch*) are also inhabitants of the lungs of sheep, the last-named causing pseudotuberculosis. *Str. commutatus* and *Str. pusillus* occur in the lungs of the hare and rabbit; *Str. syngamus* and *bronchialus* in the trachea of birds; and excite inflammations. *Str. micrurus* (*Strose*, "Bau von Strongylus micrurus," *Deut. Zeitschr. f. Thiermed.*, xviii., 1892) occurs in cows and calves, in arterial aneurisms as well as in the respiratory passages.

Strongylus pusillus causes in cats a pulmonary disease resembling tuberculosis (*Jeanmaire*, "Ueber die hist. Veränd. der Lunge bei der verminösen Pneumonie

der Katze und des Hasen," Inaug.-Diss., Freiburg, 1900). *Syngamus trachealis* (*Klee*, " Der ge paarte Luftröhrenwurm des Gaflügels," *Deut. Thierärzt. Wochenschr.*, 1899) is a dangerous parasite of birds, particularly of pheasants, in the trachea of which it appears in great numbers, and attaches itself to the mucous membrane. It is easily recognized by its red color. Similar to the last-named is *Syngamus bronchialis,* which has been observed a few times in geese and ducks.

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(*Anchylostoma and Strongylus.*)

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Ward: Nematoda. Ref. Hdb. of Med. Sc., 2d ed., vol. vi.

Fig. 531.—*Anguillula intestinalis.*
(After Braun.)

Fig. 532.—Female of *Anguillula stercoralis,* with eggs and embryos. (After Perroncito.) × 85.

§ 199. **Anguillula intestinalis** (Fig. 531) is a worm of 2.25 mm. length, which is found in the intestine, particularly in the *tropics,* and in *Italy,* and has been occasionally observed in Switzerland, Germany, Belgium, and Holland (probably transported from Italy), under similar

conditions as the Anchylostoma duodenale. According to the observations of Leuckart, Golgi, Grassi, Leichtenstern, Zinn and others, the *Anguillula intestinalis* is a hermaphrodite, the eggs of which develop even in the intestine to embryos of 0.2 mm. in length; and, in the presence in the intestine of numerous parent-worms, are found in the fæces in great numbers. In the stools they become changed in about twelve hours into filaria-like larvæ, which, when gaining entrance into the human intestine, again grow into parasitic anguillulæ, which are in turn able to produce eggs capable of development. In addition there also occurs development with an intermediate sexual generation, a heterogony.

FIG. 533.

FIG. 534.

FIG. 533.—*Tricocephalus dispar.* (After Küchenmeister and Zürn.) *A*, Male; *B*, caudal end of female; *a*, cephalic end; *b*, anterior portion of body with œsophagus; *c*, stomach; *d*, intestine; *e*, cloaca; *f*, seminal duct; *g*, penis; *l*, bell-shaped penis-sheath, with end of penis; *m*, intestine of the female; *n*, anus; *o*, uterus; *p*, vaginal opening. × 9.

FIG. 534.—Egg of *Tricocephalus dispar*. (After Hellar.) × 315.

In the event of sexual development the embryos grow outside the body in about three days into sexually mature animals (female 1.2 mm. long, male 0.88 mm.) which are known as *Anguillula* or *Rhabditis stercoralis* (Fig. 532), and were formerly regarded as a separate species. The embryos of the separate sexual individuals develop into filaria-like larvæ, which, entering the intestine of man, again grow into parasitic anguillulæ.

According to Leichtenstern and Zinn the filaria-like larvæ of direct development are more resistant than those of the sexual. The sexual mode of multiplication occurs particularly in the anguillula, coming from the tropics, while in the indigenous form (brick-laborers of Germany, Belgium, Holland) direct metamorphosis predominates. Leichtenstern explained this by the assumption that the tropical anguillula, after transportation into a temperate zone, adapts itself to the less favorable climatic conditions of the latter in such manner that the anguillula of the temperate zone favors the simpler mode of development which is the more independent of the climate — namely, the direct transformation of the embryo into the filaria-shaped larvæ, which in turn grow directly into parasitic anguillulæ.

According to the statements of various authors Anguillula stercoralis, when present in large numbers, causes diarrhœa. According to Normand, Grassi, Golgi, Leichtenstern, and others, the worms are found chiefly in the upper parts of the small intestine. According to Leichtenstern and Askanazy the mature animals and the larvæ penetrate not only into the crypts of Lieberkühn, but also into their epithelium and into the connective tissue of the mucosa, and in cases may break through the muscularis mucosæ. The mother animals lay their eggs in the intestinal crypts. The embryos when hatched wander out into the intestine.

Literature.

(*Anguillula Stercoralis and Intestinalis.*)

Thayer: On the Occurrence of Strongyloides Intestinalis in the United States. Journ. of Exp. Med., 1901.

§ 200. **Tricocephalus dispar** (*Trichuris, trichuria*), the *whipworm,* is a common and relatively harmless parasite, though according to Askanazy it sucks blood from the intestinal mucosa. It inhabits the cæcum and the neighboring portions of the intestine. It is found also in domestic animals. The male and female are about 4–5 cm. in length (Fig. 533). The anterior body-half (*a, b*) is thin, thread-like; the posterior, which bears the sexual organs (*f, g, l, o, p*), is much thicker, in the female (*B*) cylindrical, in the male (*A*) rolled up and provided with a spiculum (*g*).

The eggs (Fig. 534) are an elongated oval, 50 μ long, and possess a thick brown shell, which shows at both poles a peg-shaped, glassy swelling.

The first stage of development of the embryos takes place in water and moist earth. It advances slowly, even in summer lasting four to five months, and in the colder months of the year much longer. The eggs are resistant to cold and drying. (For the literature see *Huber,* "Bibliographie der klin. Helminthologie," München, 1893, p. 213; *Askanazy,* "Der Peitschenwurm," *Deut. Arch. f. klin. Med.,* 57 Bd., 1896; *Heine,* "Anatomie d. Tricocephalus," *Cbl. f. Bakt,* xxviii, 1900).

§ 201. **Trichina spiralis** occurs in two forms — the trichina of the intestine and the trichina of the muscles.

The **intestinal trichina** (Fig. 535) is the sexually mature form, and is a small, white, hair-like worm scarcely visible to the naked eye. The female (*A*) is 3 mm. long, the male (*B*) is much smaller. The posterior part of the body is elongated in both sexes, and in the male (*B*) is provided on the dorsal half with two conical terminal pegs, which are directed toward the belly and are separated from each other by four knob-like papillæ. Instead of a spiculum the muscular cloaca is protruded outward during copulation.

The intestinal canal begins with a muscular mouth, and this, becoming wider, passes into the œsophagus, which throughout its length is surrounded by the so-called cell-body — that is, by rows of large cells. The stomach, which follows the œsophagus, is a flask-shaped dilatation of the intestine, and is lined with finely granular cells. The stomach passes without essential change of structure into the intestine, which in the male unites with the seminal duct at the posterior end to form the cloaca.

The testicles consist of a pouch, which begins near the caudal end as a blind sac, proceeds as far forward as the cell-bodies, and bending there, passes over into the seminal duct.

The sexual organs of the female (*A*) consist of a single ovary, a uterus and a vagina, which opens externally at the junction of the first and second quarters. The ovary likewise forms a pouch lying close to the posterior end of the body, in which the round eggs develop. The pouch passes anteriorly into the sac-shaped *uterus.*

The eggs develop in the uterus into embryos which are set free at birth.

The **muscle-trichina** (Fig. 536) is a worm 0.7–1 mm. in length, which lives in the muscles of the body. It is usually rolled into a spiral and lies in a capsule, which occasionally contains lime-salts. Between the coils of the worm there is a finely granular mass.

A single capsule may contain three to five trichinæ.

If a piece of muscle containing living trichinæ is taken into the stomach of a host — for example, man — the capsule is dissolved and the trichinæ are set free. In the intestinal canal they attain sexual maturity within two and a half days, when copulation takes place. On the seventh day after the ingestion of muscle trichinæ the birth of em-broyos begins, and continues some time, even for weeks. A single female trichina may bear from one thousand to thirteen hundred young. According to Pagenstecher, Chatin, Cerfontaine, and Askanazy, the female trichinæ penetrate into the intestinal villi and deposit the embryos in the chyle-vessels, whence their migration begins. To what extent they are swept along passively by the lymph, or to what extent active migration is concerned in their spreading, is difficult to determine. When arriving in the muscles they penetrate the primitive fibres, cause the adjacent contents of the fibre to degenerate, and grow in about fourteen days to fully developed trichinæ. In the neighborhood of the trichinæ there occurs proliferation of muscle-nuclei. At first the muscle-trichinæ are enclosed only by the sarcolemma, which appears thickened and hyaline about them. Later there occurs in the neighborhood inflammatory proliferation of granu-lation tissue which leads to the production of con-nective tissue on the outside of the sarcolemma and penetrates even within the sarcolemma tube, the muscle-nuclei being destroyed. Fat-cells may appear later in the connective tissue of the cap-sule, the development of the latter being especially marked at the poles.

The intestinal trichinæ have a limited life of from five to eight weeks. The muscle-trichinæ, on the other hand, may live for long, possibly an un-limited time — that is, until death of the affected individual; at any rate for years, although, accord-ing to Ehrhardt, a few may die before encapsula-tion. After some time there frequently occurs de-position of lime-salts in the capsule, especially at the poles, causing it to appear glistening-white by reflected light, and cloudy and dark by transmitted light. In rare cases the trichinæ after dying be-come calcified.

Trichinæ have been observed, besides in man,
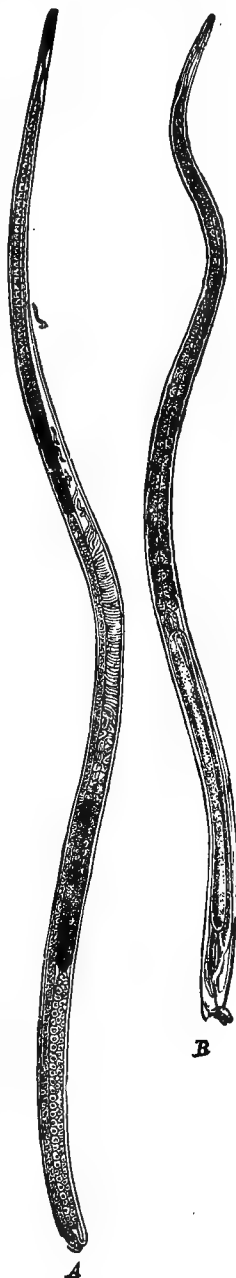
FIG. 535.—Sexually mature trichinæ. *A*, Female; *B*, male. (After Leuckart.) × 120.

in the hog, cat, dog, rat, mouse, marmot, polecat, fox, marten, badger, hedgehog, and raccoon. Through feeding of trichinous meat muscle-trichinæ may be developed in rabbits, guinea-pigs, sheep, dogs, etc. Man becomes infected through eating uncooked pork. The invasion of trichinæ produces various phenomena in man. The introduction of trichinous meat into the intestine is followed by the symptoms of intestinal catarrh. With the invasion of the muscles there are produced pain, swelling, œdema, paralysis, and not infrequently fever. In the blood there occurs

FIG. 536.—Encapsulated muscle trichinæ. (After Leuckart.) × 60.

marked increase of eosinophile cells (Opie, Schleip). The symptoms are most severe in the fourth and fifth weeks. Death not infrequently results. The intensity and severity of the symptoms depend on the number of worms wandering into the muscles.

The trichinæ are found most abundantly in the diaphragm, tongue, intercostal muscles, the muscles of the neck and larynx, the lumbar muscles, and are scattered most sparsely in the distant muscles of the extremities. They are usually most numerous about the insertions of tendons.

According to *Frothingham* (*Jour. of Med. Res.*, 1906), the trichina embryos are found in the sinuses of the mesenteric lymph-nodes and in the liver sinusoids, showing that they enter the lymph-stream and are distributed by the circulating blood. Trichina embryos are found in the areas of hæmorrhage occurring in the lungs. Local destruction of tissue may take place in the liver, pancreas, brain, and heart as a result of the parasite leaving the blood-vessel. The capsule of the encysted trichinæ is formed of connective tissue which surrounds the whole of the invaded fibre.

Staübli, in 1905, recovered embryos from the heart's blood of infected guinea-pigs by laking a small quantity of blood with 3 per cent acetic acid, certifugalizing, and examining the sediment. This method has since been successfully employed by *Herrick* and *Janeway* in human infection. In view of the fact that examination of the fæces is practically always fruitless and since consent for the removal of a portion of muscle for histological examination is not always to be obtained, this method of diagnosis is of particular value. *Staübli*, Verhandlung des Kongress f. klin. Med., Wiesbaden, 1905; *Herrick* and *Janeway*, Archives Internal Medicine, 1909.)

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(*Trichina Spiralis; Trichinosis.*)

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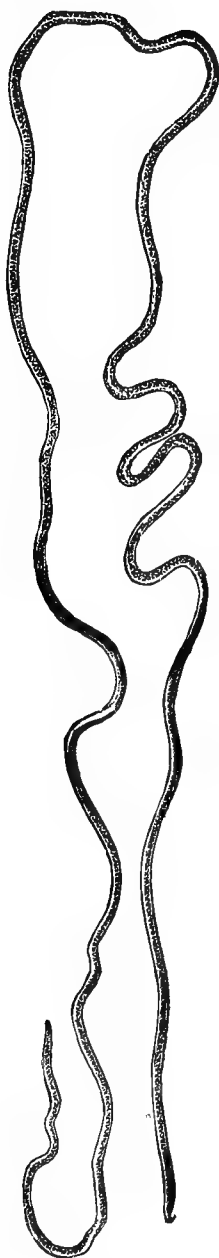
FIG. 537. FIG. 538.

FIG. 537.—*Filaria* sive *Dracunculus medinensis.*
(After Leuckart.) Natural size

FIG. 538.—Embryo of *Filaria Bancrofti,* known
as *Filaria sanguinis hominis.* (After Lewis.) ×
400.

§ 202. **Filaria** or **Dracunculus medinensis,** the Guinea-worm (Fig. 537), is a thin, thread-like female worm from 60 to 100 cm. in length. The males (observed by Charles) which were attached to female filariæ, were only 4 cm. long. The anterior extremity is rounded off, while the posterior tapers into a pointed tail which is curved toward the belly. The external covering consists of a firm cuticle, which at the cephalic end is thickened in the form of a shield. The intestinal canal is narrow and has no anus. The uterus, filled with young, takes up nearly the whole of the body-cavity. The embryos, which are set free by bursting of the mother-worm, have a firm cuticle and an awl-shaped tail. As intermediate host, the embryos seek out small crustaceæ, in which they are probably taken into the stomach of man with drinking water. In Africa and Asia the worm is of frequent occurrence. It developes in the skin to sexual maturity and causes abscesses of the affected region. It is usually found on the lower extremities, especially in the region of the heels.

Filaria sanguinis hominis is the name given to *larvæ* (Fig. 538) that occur in the blood and lymph of man, and are about 0.35 mm. in length. The sexually mature worm is filiform, the male about 8 cm. long and the female 15 cm. It is called **Filaria Bancrofti** after its discoverer. The worm inhabits the lymph-vessels, particularly those of the scrotum and lower extremities, and may be present in large numbers. It causes lymph-stasis and inflammations which lead to *swelling of the lymph-nodes* and to *elephantiasis-like thickening of the tissue,* associated with œdema and lymphangiectasis. Purulent inflammation, lymph-abscesses, buboes, chylous hydrocele, and chylous ascites may appear in consequence of its presence.

From the lymphatics of the limbs and scrotum the eggs and embryos (0.35 mm. long) (Fig. 538) pass into parts of the lymphatic system and into the blood, giving rise to hæmaturia, chyluria, and chylous diarrhœa. According to Manson and Scheube the filariæ are present in blood

taken from the skin only during the night; von Linstow explains this phe-
nomenon as due to the fact that during sleep the peripheral vessels
become dilated, and so permit the entrance of the filariæ, while the capil-
laries, being narrower during the day, do not permit such entrance. The
hæmaturia is the result of the collection of embryos in the blood-vessels
of the urinary tract. The chyluria and the chylous diarrhœa, on the other
hand, are due to obstruction by the parasites of the thoracic duct, thus
causing lymph-stasis which extends to the lymphatics of the bladder and
intestine and there occasions the escape of lymph. According to
Scheube rupture of the lymphatics is attended by rupture of blood-
vessels, so that blood becomes mixed with the lymph. The embryos may
pass out through the urine.

The distribution of the embryos is, according to Manson, accomplished
by means of mosquitoes, which take up the parasite during the act of
blood-sucking. In the mosquitoes they pass through a second stage of
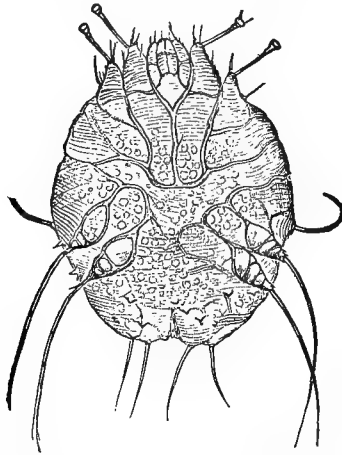
Fig. 539.—Female itch-mite, ventral surface.
× 40.

development and are then (James) after two or three weeks ready for
the infection of a new host. Manson formerly held the opinion that they
entered the water, and in a free condition were taken up in the water into
the intestinal tract. The investigations of James, Low, Grassi, and Noè,
who followed their development and migration in the body of mosquitoes,
make it probable that they are transmitted to a new host through the bite
of the mosquito.

The Filaria sanguinis occurs most commonly in the tropics (Brazil,
Egypt, Algiers, Madagascar, Zanzibar, Soudan, South China, Calcutta,
Bahai, Guadeloupe), sometimes in the Southern States.

Of the **Acanthocephala**, nematode-like worms having no intestine, and
possessing at the anterior end a retractile proboscis set with hooklets, the
most important is the *Echinorhyncus gigas*. The male is 10–15 cm. long,
and the female 30–50. It occurs chiefly in the intestine of the pig, and
penetrates into the intestinal wall. According to Lindemann, it occurs
occasionally in man. The rose chafer and the May beetle serve as inter-
mediate hosts.

Mackenzie estimated the number of filaria-embryos present in the total bulk of the blood of a case of hæmatochyluria studied by him at from thirty-six to forty millions. The patient died from empyema; during the disease the filariæ died.

In **domestic animals** numerous *filaria-species* occur and inhabit different parts of the body. *Filaria papillosa* is a common parasite of the horse, donkey, and cattle; it lives in the serous cavities and reaches a length of from 5–18 cm. *Filaria hæmatica,* a worm 3–13 cm. long, inhabits the right heart and the pulmonary artery
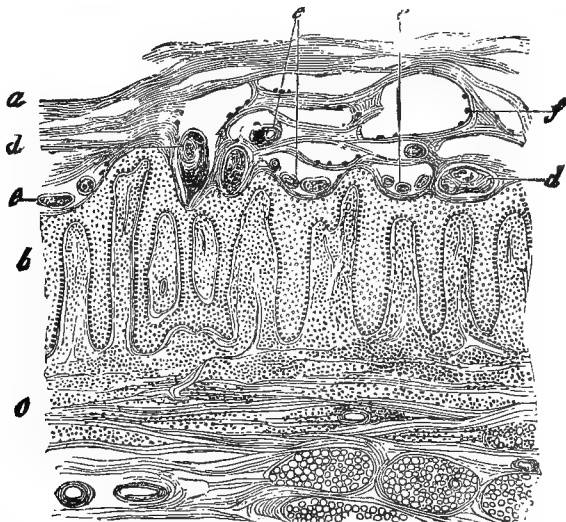
FIG. 540.—Scabies (alcohol, carmine). *a,* Horny layer of the epidermis, perforated by numerous burrows of the itch-mite; *b,* mucous layer, and papillary body, the latter greatly enlarged and infiltrated with cells; *c,* cutis infiltrated with cells; *d,* section through a fully developed itch-mite; *e,* eggs and embryos of different sizes; *f,* fæces. × 20.

of the dog, and in this situation gives off its embryos to the blood-stream. It occurs particularly in America, China, and India. *Filaria hæmorrhagica* or *multipapillosa* causes a nodular cutaneous affection in the horse and donkey.

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III. Arthropoda.

1. Arachnida.

§ 203. The parasites included among the **Arachnida** are chiefly epizoa, which either temporarily or permanently inhabit the skin. Only one species — *Pentastoma* — occurs in the larval form in the tissues. The most common parasites of this group belong to the *Mites* (*Acarina*). The pentastoma belongs to the family of *tongue-worms* (*Pentastomidæ* or *Linguatulidæ*).

(1) **Acarus scabei** or **Sarcoptes hominis,** the **itch-mite,** is the size of a pinhead with a turtle-shaped body, provided on the ventral surface
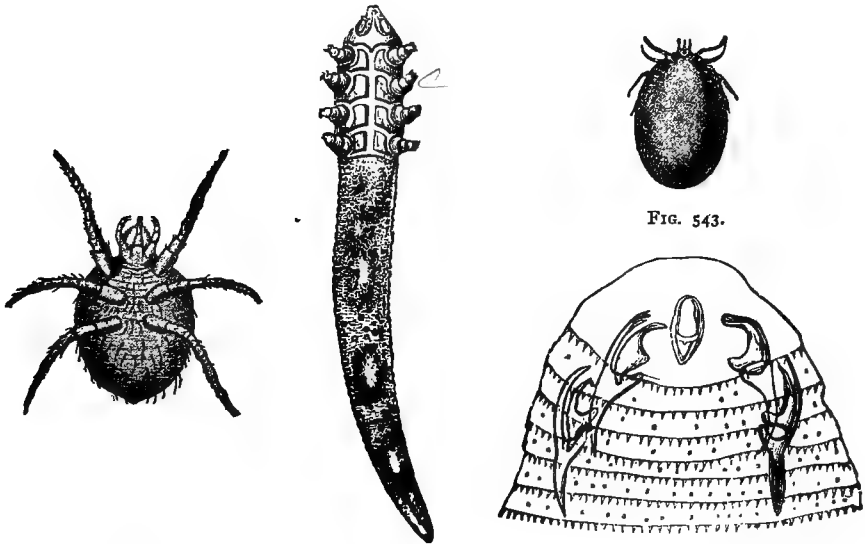
Fig. 543.

Fig. 541.   Fig. 542.   Fig. 544.

Fig 541.—*Leptus autumnalis.* (After Küchenmeister and Zürn.)

Fig. 542.—*Acarus folliculorum hominis.* (After Perls.) × 300.

Fig. 543.—*Ixodes ricinus,* sucked half full of blood. × 2.

Fig 544.—Cephalic end of *Pentastoma denticulatum.* (After Perls.) × 40.

both anteriorly and posteriorly with two pairs of legs, each of which is furnished with bristles (Fig. 539). The anterior pairs of legs extend out into pedicled clinging-discs. The same arrangement is found in the posterior two pairs in the male, while in the female both of the posterior pairs end in long bristles. Several bristles are also found along the border of the posterior portion of the body, while the back is studded with tooth-like knobs. The head is round and likewise set with bristles. The female is nearly double the size of the male.

The mite lives in the epidermis (Fig. 540, *a, d*), in which it forms burrows, some of which are 10 cm. long.

In the burrows the female (*d*) lays the eggs, which develop *in situ* into the young itch-mites (*e*), which penetrate still deeper into the epi-

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dermis, and after repeated sheddings of their skins grow into sexually mature animals. The skin responds to the irritation produced by the presence of the mites by increased production of epithelial cells (*a*) and inflammation (*c*). The latter is further increased through the scratching of the spots which itch in consequence of the invasion.

2. **Leptus autumnalis,** the *harvest-mite* (Fig. 541) is the red-colored larva of a variety of *Trombididæ,* which lives on grasses and bushes and on grain, and when occasion offers alights on the skin of man, where it penetrates the epithelium and causes itching and inflammation.

3. **Demodex** or **Acarus folliculorum hominis** (Fig. 542) occurs either singly or in numbers in the hair-follicles of the face, as well as in the ducts of the sebaceous and Meibomian glands. Hausche found the demodex on the eyelashes in seventy-nine per cent., and Joers in sixty-four per cent. of the cases examined. Children under one year of age were free. The female is 0.4 mm. long, the male 0.3 mm. The eggs are deposited on the shaft of the hair or on any other portion of tissue, and develop after two sheddings into sexually mature animals which are found in the entrances to the hair-follicles and sebaceous glands, with their heads directed inward. The assumption that the demodex causes inflammation (acne, blepharitis acarica) is not supported (Joers, Hausche), since in spite of its presence in the great majority of cases signs of inflammation are wanting.

It has on its anterior ventral surface (Fig. 542) four pairs of short thick feet. The head possesses a snout and two feelers.

4. **Ixodes ricinus,** the *wood-jack* or *wood-tick* (Fig. 543), is a fairly large yellowish-brown member of the Arachnida belonging to the ticks. It has a black head provided with a sucking apparatus, and a distensible leathery body. It is of common occurrence on grass and bushes, and sometimes alights on man or beast. By means of its sucking apparatus it draws blood from the skin and swells to a remarkable extent.

5. **Pentastoma denticulatum** is the larva of **Pentastoma tænoides,** a lancet-shaped animal belonging to the tongue-worms or *Pentastomidæ.* It inhabits the nasal, frontal, and maxillary cavities of various animals, especially of the dog, rarely of man (Laudon) and occasions inflammations. The female of the mature animal is 50–80 mm. long, and anteriorly from 8–10 mm. broad; the male is 16–22 mm. long, and anteriorly from 3–4 mm. broad. The body consists of eighty-seven to ninety segments, the most anterior of which bear lateral segment-appendages, the pairs of limbs. The eggs, which are produced in great numbers, are oval. The larva is 4–5 mm. long, 1.5 mm. broad, plump, flattened, and inhabits chiefly the liver, lung, or spleen, or more rarely the other organs of man and the herbivora. It occurs in the form of a small nodule encapsulated in connective tissue. The body consists of about fifty ring-shaped segments which are provided at the borders with spines (Fig. 544), and the cephalic end is provided with four hook-shaped feet. The eggs are taken in from the external world through the intestinal tract. The parasites set free in the intestine wander by means of a boring apparatus through the mesentery into the mesenteric lymph-nodes, or penetrate directly into blood-vessels, and are carried to the liver or even to the lumgs, where after shedding they develop into the encysted larvæ. The larvæ may in their wanderings gain access to the nasal cavity of their host, and develop into mature animals, although the further development usually takes place only after their reception into a new host.

According to the published reports of Tanaka a small red mite occurs in great numbers in different parts of Japan during midsummer, and clinging firmly to the skin of man causes the so-called *Kedani-disease*, which is characterized by inflammation of the skin and lymph-nodes, with high fever, and often ends fatally. It is probable that these symptoms are due to secondary infections (proteus and streptococci) in the bites of the mite. *Argus reflexus*, a tick, causes by its bite not only local inflammation, but nausea, diarrhœa, cardiac palpitation, asthma, etc., through a poison derived from its salivary glands. It is found also in pigeons.

In **domestic animals** living **mites** occur frequently as parasites of the skin, and represent different species of various families (*Sarcoptides, Dermatocoptes, Dermatophages,* and *Acarides*).

Sarcoptes hominis, the *burrow-mite* or *itch-mite* of man, is also found in horses and Neapolitan sheep. In addition still other different species of sarcoptes may be distinguished as parasites of the domestic animals — for example, *Sarcoptes squamiferus* in dogs, hogs, sheep and goats, and *Sarcoptes minor* in cats and rabbits.
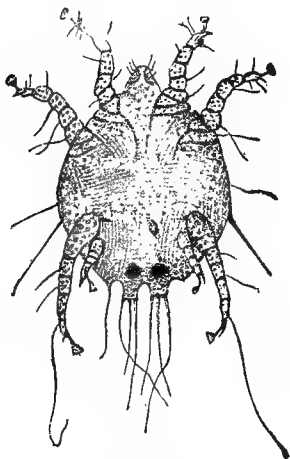
FIG. 545.

FIG. 546.

FIG. 545.—Male of *Dermatophagus communis* seen from the ventral side. (After Pütz.) × 50.
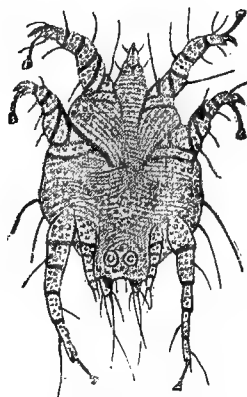
FIG. 546.—Male of *Dermatocoptes communis,* seen from the ventral side. (After Pütz.) × 50.

Dermatophagus, the *devouring-mite* (Fig. 545), with a broad head, occurs in different animals, and different species may be distinguished. It lives on the cells of the epidermis and causes desquamation of the skin.

Dermatocoptes, the *sucking-mite* (Fig. 546), with long narrow head, takes blood and lymph from the skin and causes inflammation. *Dermatocoptes communis* occurs in horses, cattle, and sheep.

Dermatocoptes cuniculi is a parasite of the rabbit's ear, and causes the ear-scab which usually occurs on the inner side of the auricle.

Symbiotes equi of *Gerlach* is a mite which occurs chiefly on the feet of the heavy English and Scotch horses, and causes a moist dermatitis, often incorrectly called *malanders.*

Dermanyssus avium is a long, red, blood-sucking mite, about 1 mm. long, and is often found on birds.

Dermatoryctes mutans causes the foot-itch of chickens whereby the skin acquires a mortar-like scabby covering.

Acarus folliculorum or *Demodex folliculorum,* the mite of the hair-follicles, occurs most frequently in the dog or cat, more rarely in the hog, cattle, and the goat. In the dog it causes the formation of scales, falling out of the hair, and a pustular eruption.

Demodex phylloides causes in swine nodular inflammations and ulcers particularly on the snout, neck, breasts and flanks, and the inner surface of the thighs. The purulent foci contain great numbers of the mites. The mite may develop also on cattle.

Various species of *Ixodes* of the tick family occur on dogs, cattle, and sheep; *Argas reflexus* occurs on pigeons; and other forms of ticks occur on the domestic animals.

Leptus autumnalis occurs also on dogs and chickens.

Pentastomata occur also in cattle, sheep, and goats, and in certain regions are very common in the first-named.

2. Insecta.

§ 204. The parasites belonging to the class of *Insecta* are for the greater part epizoa. In part they are but transient inhabitants of the skin, deriving from it their nourishment; in part they are permanent inhabitants and utilize the skin structures for the deposit of their eggs. Of the numerous species belonging to this class the following may be mentioned:

(1) **Pediculus capitis,** the head-louse (Fig. 547), inhabits the hairy portions of the head, and derives its nourishment (i.e., blood) from the skin, by means of its feeding apparatus. Its eggs (nits) are barrel-
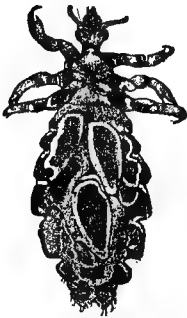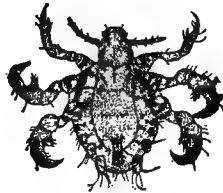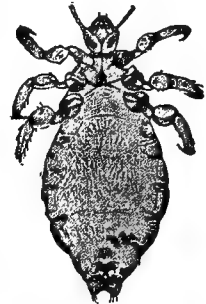
FIG. 547.   FIG. 548.   FIG. 549.

FIG. 547.—Female of *Pediculus capitis,* seen from the ventral surface. (Küchenmeister and Zürn.) × 13.

FIG. 548.—Male of *Pediculus pubis,* seen from the ventral surface. (Küchenmeister and Zürn.) × 13.

FIG. 549.—Female of *Pediculus vestimentorum,* seen from the ventral surface. (Küchenmeisten and Zürn.) × 9.

shaped and white, and are attached to the hairs by means of a chitinous shell. The embryo hatches in about eight days. In consequence of the scratching induced by the itching there often arise inflammations of the skin, in particular eczemas, which are often severe.

(2) **Pediculus pubis** (*Phthirius inguinalis*), the *felt* or *crab-louse* (Fig. 548), inhabits the hairy parts of the trunk and extremities. Its habits of life are the same as those of *Pediculus capitis.*

(3) **Pediculus vestimentorum,** the *clothing* or *body-louse* (Fig. 549), lives in the wearing apparel, and lays its eggs in the same. It gets on man to obtain its nourishment.

(4) **Cimex lectularius,** the bedbug, dwells in beds, floors, closets, etc. During the night it gets on man to suck blood. It causes wheals in the skin.

(5) **Pulex irritans,** the *common flea,* also draws blood from the skin. At the point where it has sucked there is found a little punctate hæmorrhage. Occasionally it causes wheals and swellings. It lays its eggs in the cracks of floors, in sawdust, etc.

(6) **Pulex penetrans** (*Sarcopsylla penetrans*), the *sand flea,* occurs in South Africa in the sand. The female lays her eggs in the skin thereby causing intense inflammation.

(7) **Mosquitoes** provided with stinging and sucking apparatus (*Culicidæ* and *Tipulidæ*), **horse-flies** (*Tabanidæ*), and **flies** (*Stomoxyidæ*) draw blood frequently from the skin of man. Various **flies** (*Œstridæ,* biting bot-flies, *Muscidæ* or *blow-flies*) occasionally lay their eggs in the skin, in ulcers or wounds, or in the accessible body-cavities, in consequence of which the maggots developing cause local destruction of tissue and inflammation (*myiasis*). Under certain conditions their larvæ (for example, that of *Anthomia canicularis,* Fig. 550) may get into the
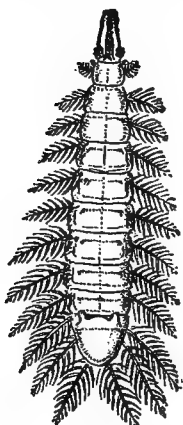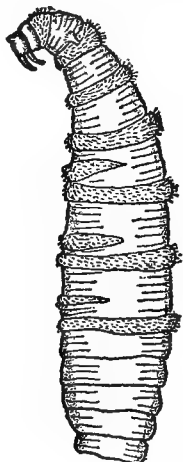
Fig. 550.   Fig. 551.   Fig. 552.   Fig. 553.
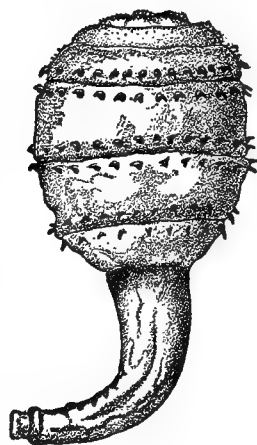
Fig. 550.—Larva of *Anthomia canicularis.* (After Braun.) About × 6.

Fig. 551.—Larva of *Musca vomitoria.* (After Braun.) About × 6.

Fig. 552.—Larva of *Lucilia macellaria.* (After Braun.) About × 6.

Fig. 553.—Larva of *Dermatobia cyaniventris.* (After Blanchard.) About × 6.

intestinal tract with the food and there undergo further development (*myiasis intestinalis*). This is especially likely to occur when abnormal conditions which interfere with digestion are present in the stomach and intestine. The *eggs of the Muscidæ* (in Europe usually of *Sarcophila wohlfarti* and *Musca vomitoria* [Fig. 551], in America of *Compsomyia* or *Lucilia macellaria* [Fig. 552], and *Musca anthropophaga*), when laid on the mucous membranes or in wounds, hatch after a few hours, and cause destruction of the neighboring soft parts through their efforts to obtain nourishment. In the auditory canal, nose, and antrum of Highmore the bones may be laid bare (*myiasis mucosa*). In the course of about a week the larvæ leave the ulcers and pass into the pupa stage in the earth. The *Œstridæ* (in Europe, *Hypoderma bovis* and *Hypoderma diana;* in America, *Dermatobia cyaniventris* [Fig. 553] or *Cuterebra noxialis*) lay their eggs on wounds or in the intact skin. The larvæ, hatching soon, penetrate into the cutis by means of their hooklets, and after several sheddings grow in from one to six months into larger larvæ about 2 cm. long. They cause, particularly in their later stages, painful swellings of the neighboring tissue (*myiasis œstrosa*).

Parasites belonging to the *Muscidæ* and *Oestridæ* play a more important rôle in the case of the domestic animals than in man; and the larvæ of the species of *Oestrus* in particular occur as parasites in animals. For example, the larvæ of *Gastrophilus equi* (Fig. 554), *Gast. pecorum* and *Gast. hæmorrhoidalis* inhabit the stomach and adjacent portions of the intestinal tract of the horse, where they complete their development up to the pupa-stage, when they leave the animal.

Oestrus ovis lays its larvæ in the nasal cavities of sheep, whence they may wander, under certain conditions, into the frontal, nasal, and maxillary cavities, or even into the cranial cavity, and excite inflammation.

Hypoderma or *Oestrus bovis*, the biting fly, or bot-fly, lays its eggs on the skin of cattle. The larva bores into the skin and enters the spinal canal of cattle, completing here its development up to the pupa-stage, at which time it leaves the animal. According to *Schneidemühl*, the larvæ do not always enter through the skin, but are often taken in with the food, whereupon they penetrate through the wall of the œsophagus toward the skin and spinal canal. The latter follows from the fact that they are found in the

FIG. 554.—*Gastrophilus equi.* (After Brauer.)
a, Male; b, larva.

wall of the œsophagus from October to January, and under the skin, on the other hand, from January to April. In the skin they cause the so-called "fly-boils."

Sarcophila wohlfarti (*Sarcophaga magnifica*) lays its larvæ on the skin of horses, sheep, cattle, dogs, and geese. *Lucilia macellaria* lays its eggs between the hind legs of lambs suffering with diarrhœa. The larvæ seek the thick-wooled portions of the root of the tail and the lumbar region and bore into the skin.

GENERAL INDEX.